Moss Pharmacy and Nutrition Center
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R.T. (TENNY) MOSS, JR.
Pharmacist - Chemist

June 4, 1998

Dockets Management Branch (HFA-305)
Food and Drug Administration
1240 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

98 JUN -8 A11:57 1210

Dear Sirs:

As per Section 127 of the Food and Drug Administration Modernization Act of 1997, I am nominating 21 bulk drug substances as candidates for the bulk drug list. You will find folders on each of these substances inclosed in this package.

There are eight people on the South Carolina Board of Pharmacy. There are five practicing pharmacists who as a regular aspect of their practice compound medications on a daily basis: Davis Hook, Hugh Mobley, Charles Turner, Ronnie Cromer, Bubby Hutto. When I am added to that group there is a total of six board members out of eight who are compounding pharmacists. My nominations reflect some of the drug products that we board members, as well as other South Carolina pharmacists, use in preparing prescriptions with drug substances that are not USP or NF substances.

Out of the products I am submitting, this past week week I compounded the folowwing prescriptions: Caffeine Citrated for a newborn released from a local hospital, Ferric Subsulfate Solution for a local physician to treat a patient, Metronidazole Benzoate suspensions for a little girl and a bird, Quinacrine Capsules for three women, and Piracetam for a young girl with Downs Syndrome. I don't use these substances every day, but I or another South Carolina pharmacist <u>have</u> used every one of these substances for our patients.

On behalf of the public we serve and the pharmacists of this state I request that these drug substances be approved and appear on the list of bulk drug substances that may be used in compounding.

Regards,

Tenny Moss

Robert T. Moss, Jr.

98N-0182

NOM 7

A. INGREDIENT NAME:

AMINOPYRIDINE

B. Chemical Name:

Amino-4 Pyridine, Fampridina. 4-Aminopyridine; 4-Pridinamine

C. Common Name:

Gamma-Aminopyridine, P-Aminopyridine, P-Aminopyridine (DOT), 4-AP, Avitrol, Avitrol 200, 4-Pyridylamine, 4-Pyridinamine, Fampridine

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.3%

E. Information about how the ingredient is supplied:

White crystals, or crystalline powder, odorless.

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Agoston, S. Antoagonism of ketamine-diazepam anaesthesia by 4-Aminopyridine in human volunteers. *Br J Anaesth,* 1980; 52: 367-370.

Evenhuis, J. Pharmacokinetics of 4-aminopyridine in human volunteers. *Br J Anaesth,* 1981; 53: 567-569.

Ter Wee, P. M. 4-Aminopyridine and haemodialysis in the treatment of verapamil intoxication. *Hum toxicol,* 1985;4:327-329.

Agoston, S. Effects of 4-aminopyridine in Eaton Lambert syndrome. *Br. J Anaesth,* 1978; 50: 383-385.

Davis, F. A. Orally administered 4-aminopyridine improves clinical signs inmultiple sclerosis. *Ann Neurol,* 1990;27: 186-192.

Bever, C. T., Young, D. and Anderson, P. A. The effects of 4-aminopyridine inmultiple sclerosis patients; results of a randomized, placebo-controlled, double blind, concentration-controlled, crossover trial. *Neurology,* 1994; 44: 1054-1059.

Segal, J. L. and Brunnemann, S. R. 4-Aminopyridine improves pulmonary function in quadriplegic humans with longstanding spinal ord injury. *Pharmacotherapy,* 1997; 17(3): 415-423.

Schwid, S. R., Petrie, M. D., and McDermott, M. P. Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis. *Neurology,* 1997; 48(4): 817-821.

Chang, F. C., Bauer, R. M.,and Benton, B. J. 4-aminopyridine antagonizes saxitoxin and tetrodotoxin induced cardiorespiratory depression. *Toxicon,* 1996; 34(6): 671-690.

Chen, H. M., Lin, C. H., and Wang, T. M. Effects of 4-aminopyridine on saxitoxin intoxication. *Toxicology & Applied Pharmacology,* 1996; 141(1): 44-48.
Perez-Espejo, M. A., Haghighi, S. S., and Adelstein, E. H. The effects of taxon, methylprednisone, and 4-aminopyridine in compressive spinal cord injury: a qualitative experimental study. *Surgical Neurology,* 1996; 46(4): 350-357.

Wananukul, W., Keyler, D. E., and Pentel ,P. R. Effect of calcium chloride and 4-aminopyridine therapy on desipramine toxicity in rats. *Journal of Toxicology,* 1996; 34(5): 499-506.

Haghighi, S. S., Pugh, S. L., Perez-Espejo, M.A. Effects of 4-aminopyridine in acute spinal cord injury. *Surgical Neurology,* 1995; 43(5): 443-447.

Li L. and Zhang, Y. P. Therapy of experimental autoimmune myasthenia gravis in rabbits with 4-aminopyridine and 3,4-diaminopyridine. *Chung-Kuo Yao Li Hsueh Pao - Acta Pharmacologica Sinica,* 1994; 15(4): 358-362.

Polman, C. H., Bertelsmann, F. W., and de Waal, R. 4-Aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis. *Archives of Neurology,* 1994; 51(11): 1136-1139.

Smits, R. C., Emmen, H. H., and Bertelsmann, F. W. The effects of 4-aminopyridine on cognitive function in patients with multiple sclerosis; a pilot study. *Neurology,* 1994: 44(9): 1701-1705.

Bever, C. T. The current status of studies of aminopyridines in patients with multiple sclerosis. *Annals of Neurology,* 1994; 36 Suppl: S118-121.

Polman, C. H., Bertelsmann, F. W., and van Loenen, A. C. 4-aminopyridine i nthe treatment of patients with multiple sclerosis. Long-term efficacy and safety. *Archives of Neurology,* 1994; 51(3): 292-296.

van Diemen, H. A., Polman, C. H., and van Dongen, M. M. 4-aminopyridine induces functional improvement in multiple sclerosis patients: a neurophysiological study. *Journal of the Neurological Sciences,* 1993; 116(2): 220-226.

Hansebout, R. R., Blight, A. R., and Fawcett, S. 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients. *Journal of Neurotrauma,* 1993; 10(1): 1-18.

Hayes, K. C., Blight, A. R., and Potter, P. J. Preclinical trial of 4-aminopyridine in patients with chronic spinal cord injury. *Paraplegia,* 1993; 31(4): 216-224.

van Diemen, H. A., Polman, C. H., and van Dongen. The effect of 4-ami pyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study. *Annals of Neurology,* 1992; 32(2): 123-130.

Nockels, R. and Young, W. Pharmacologic strategies in the treatment of experimental spinal cord injury. *Journal of aneurotrauma,* 1992; 9 Suppl 1: S211-217.

Stefoski, D., Davis, F. A., and Fitzsimmons, W. E. 4-Aminopyridine in multiple sclerosis: prolonged administration. *Neorulogy,* 1991; 41(9): 1344-1348.

Blight, A. R., Toombs, J. P., and Bauer, M. S. The effects of 4-aminopyridine on neurological deficits in chronic cases of traumatic spinal cord injury in dogs: a phase I clinical trial. *Journal of Neurotrauma,* 1991; 8(2): 103-109.

Wiseman, E. J. and Jarvik, L. F. Potassium channel blockers: could they work in Alzheimer disease? *Alzheimer Disease 7 Associated Disorders,* 1991; 5(1): 25-30.

Davis, F.A., Stefoski, D., and Rush, J. Orally administered 4-aminopyridine improves clinical signs in multiple sclerosis. *Annals of Neurology,* 1990; 27(2): 186-192.

Hansebout, R. R., Blight, A. R., and Fawcett, S. Aminopyridine chronic spinal cord injury: a controlled, double-blind, crossover, study in eight patients. *J Neurotrauma,* 1993; 19: 1-18.

Hayes, K. C., Blight, A. R., and Potter, P. J. Preclinical trail of 4-aminopyrisdine in patients with chronic spinal cord injury. *Paraplegia*, 1993; 31: 216-224.

Hayes, K. C., Potter, P. J., and Wolfe, D. L. 4-aminopyridine-sensitive neurologic deficits in patients with spinal cord injury. *J Neurotrauma*, 1994; 11(4): 433-446.

H. Information about dosage forms used:

Capsules

I. Information about strength:

10mg

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 158.9°
Strong oxidizing agents
Strong acids
Acid chlorides
Acid Anhydrides

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

50-243
42976

PRODUCT NO: 2366

PRODUCT: 4-Aminopyridine

We hereby certify that batch **18714** of the above product has been tested with the following results:

Appearance:	White crystals
Melting Point:	158-161°C
Assay (GC):	99.3%

Date of Analysis: 30 July 1993

Signed: [signature] 25 February 1997

Quality Control Manager

QUALITY CONTROL REPORT

CHEMICAL NAME.: AMINOPYRIDINE (4)

MANUFACTURE LOT NO.: 10020977

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE CRYSTALS, OR CRYSTALLINE POWDER. IS ODORLESS.

2) SOLUBILITY.:
SOLUBLE IN WATER; SOLUBLE IN BENZENE, IN ALCOHOL AND IN ETHER.

3) MELTING PIONT.:
MELTS AT ABOUT 158.9 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES AS PER IR SPECTRUM CO.SPECS.

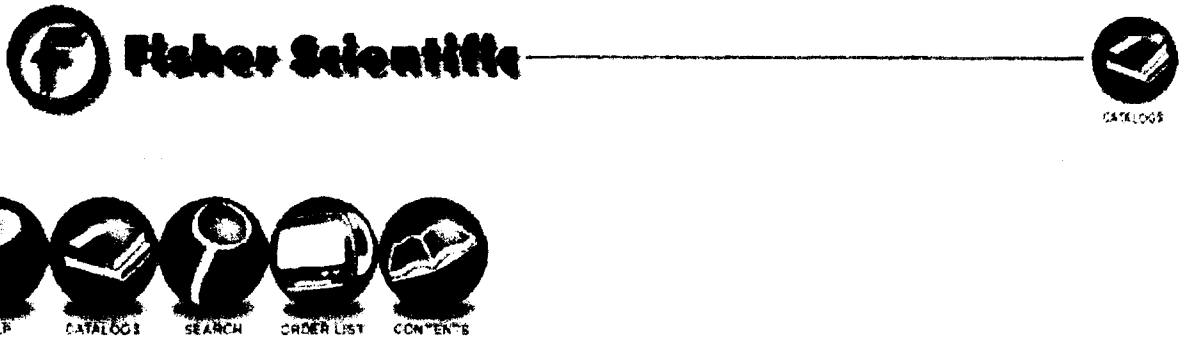
PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____



Use your web browser's "Back" key to return to previous topic.

MATERIAL SAFETY DATA SHEET

4-Aminopyridine, 98%
11601

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: 4-Aminopyridine, 98%

Company Identification: Acros Organics N.V.
One Reagent Lane
Fairlawn, NJ 07410
For information in North America, call: 800-ACROS-01
For emergencies in the US, call CHEMTREC: 800-424-9300
For emergencies in the US, call CHEMTREC: 800-424-9300

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
504-24-5	4-AMINOPYRIDINE	98%	207-987-9

Hazard Symbols: T+
Risk Phrases: 28 36/37/38

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Appearance: white.
Danger! May be fatal if swallowed. May be fatal if absorbed through the skin. Aspiration hazard. Poison! Causes eye and skin irritation. Causes digestive and respiratory tract irritation. May be fatal if inhaled.
Target Organs: Central nervous system.

Potential Health Effects

Eye:
Causes eye irritation. Causes redness and pain.

Skin:
Causes skin irritation. May be fatal if absorbed through the skin. Substance is rapidly absorbed through the skin. Causes symptoms similar to those of inhalation. Causes redness and pain.

Ingestion:
May be fatal if swallowed. May cause irritation of the digestive tract. Poison by ingestion. May cause effects similar to those for inhalation exposure.
An oral dose of 590 mg/kg of 4-aminopyridine in a man produced shortne

ss of breath, nausea, vomiting, hallucinations and distorted perceptio n. Affects the CNS to produce tremor, excitability and convulsions.

Inhalation:
Inhalation of high concentrations may cause central nervous system effects characterized by headache, dizziness, unconsciousness and coma. Causes respiratory tract irritation. May cause severe headaches, nausea, increased blood pressure, weakness, convulsions, and a stuporous state.

Chronic:
Not available.
None

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:
Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.

Skin:
Get medical aid immediately. Immediately flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:
Do NOT induce vomiting. If victim is conscious and alert, give 2-4 cupfuls of milk or water. Never give anything by mouth to an unconscious person. Get medical aid immediately.

Inhalation:
Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Notes to Physician:
Treat symptomatically and supportively.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:
As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. During a fire, irritating and highly toxic gases may be generated by thermal decomposition or combustion. Containers may explode in the heat of a fire. Combustible solid.

Extinguishing Media:
In case of fire use water spray, dry chemical, carbon dioxide, or chemical foam.

Autoignition Temperature: 640 deg C (1,184.00 deg F)
Flash Point: 156 deg C (312.80 deg F)
NFPA Rating: Not published.
Explosion Limits, Lower: Not available.
Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:
Vacuum or sweep up material and place into a suitable disposal container. Avoid generating dusty conditions. Remove all sources of ignition. Provide ventilation.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:
Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Minimize dust generation and accumulation. Do not breathe dust, vapor, mist, or gas. Do not get in eyes, on skin, or on clothing. Avoid contact with heat, sparks and flame. Do not ingest or inhale. Use only in a chemical fume hood.

Storage:
Keep away from heat, sparks, and flame. Keep away from sources of ignition. Store in a tightly closed container. Store in a cool, dry, well-ventilated area away from incompatible substances. Poison room locked.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:
Use only under a chemical fume hood.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
4-AMINOPYRIDINE	none listed	none listed	none listed

OSHA Vacated PELs:
4-AMINOPYRIDINE:
No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:
Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin:
Wear appropriate protective gloves to prevent skin exposure.

Clothing:
Wear appropriate protective clothing to prevent skin exposure.

Respirators:
Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State:	Solid
Appearance:	white
Odor:	Characteristic odor
pH:	Not available.
Vapor Pressure:	0.8 mm Hg @25C
Vapor Density:	Not available.
Evaporation Rate:	Not available.
Viscosity:	Not available.
Boiling Point:	273 deg C @ 760.00mm Hg
Freezing/Melting Point:	155 - 158 deg C
Decomposition Temperature:	Not available.
Solubility:	74 G/L (20°C)
Specific Gravity/Density:	Not available.
Molecular Formula:	C5H6N2
Molecular Weight:	94.12

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:
Stable under normal temperatures and pressures.
Conditions to Avoid:
Incompatible materials, ignition sources.
Incompatibilities with Other Materials:
Oxidizing agents, strong acids, acid chlorides, acid anhydrides
Hazardous Decomposition Products:
Nitrogen oxides, carbon monoxide, carbon dioxide.
Hazardous Polymerization: Will not occur.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
CAS# 504-24-5: US1750000
LD50/LC50:
CAS# 504-24-5: Oral, mouse: LD50 = 19 mg/kg; Oral, rat: LD50 = 21 mg/kg.
Carcinogenicity:

4-AMINOPYRIDINE -
Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.
Epidemiology:
No data available.
Teratogenicity:
No data available.
Reproductive Effects:
No data available.
Neurotoxicity:
No data available.
Mutagenicity:
No data available.
Other Studies:
No data available.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:
Bioaccumulation: none or low
Environmental Fate:
Not readily biodegradable.
Physical/Chemical:
Not available.
Other:
Not available.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
RCRA D-Series Maximum Concentration of Contaminants: Not listed.
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
RCRA F-Series: Not listed.
RCRA P-Series: waste number P008
RCRA U-Series: Not listed.
This material is banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
Shipping Name: AMINOPYRIDINES
Hazard Class: 6.1
UN Number: 2671
Packing Group: II
IMO
Shipping Name: AMINOPYRIDINES
Hazard Class: 6.1
UN Number: 2671
Packing Group: II
IATA
Shipping Name: AMINOPYRIDINES
Hazard Class: 6.1
UN Number: 2671
Packing Group: II
RID/ADR
Shipping Name: AMINOPYRIDINES
Dangerous Goods Code: 6.1(12B)
UN Number: 2671
Canadian TDG
Shipping Name: AMINOPYRIDINES
Hazard Class: 6.1
UN Number: UN2671

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL
TSCA
CAS# 504-24-5 is listed on the TSCA inventory.
Health & Safety Reporting List
None of the chemicals are on the Health & Safety Reporting List.
Chemical Test Rules
None of the chemicals in this product are under a Chemical Test Rule.
Section 12b

None of the chemicals are listed under TSCA Section 12b.
TSCA Significant New Use Rule
None of the chemicals in this material have a SNUR under TSCA.
SARA
Section 302 (RQ)
final RQ = 1000 pounds (454 kg)
Section 302 (TPQ)
CAS# 504-24-5: TPQ = 500/10,000 pounds
Section 313
No chemicals are reportable under Section 313.
Clean Air Act:
This material does not contain any hazardous air pollutants.
This material does not contain any Class 1 Ozone depletors.
This material does not contain any Class 2 Ozone depletors.
Clean Water Act:
None of the chemicals in this product are listed as Hazardous Substances under the CWA.
None of the chemicals in this product are listed as Priority Pollutants under the CWA.
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.
OSHA:
None of the chemicals in this product are considered highly hazardous by OSHA.

STATE
4-AMINOPYRIDINE can be found on the following state right to know lists: California, New Jersey, Pennsylvania, Massachusetts.
California No Significant Risk Level:
None of the chemicals in this product are listed.

European/International Regulations
European Labeling in Accordance with EC Directives
Hazard Symbols: T+
Risk Phrases:
R 28 Very toxic if swallowed.
R 36/37/38 Irritating to eyes, respiratory system and skin.
Safety Phrases:
S 1 Keep locked up.
S 37/39 Wear suitable gloves and eye/face protection.
S 45 In case of accident of if you feel unwell, seek medical advice immediately (show the label where possible).
S 28A After contact with skin, wash immediately with plenty of water.

WGK (Water Danger/Protection)
CAS# 504-24-5:

Canada
CAS# 504-24-5 is listed on Canada's DSL/NDSL List.
This product does not have a WHMIS classification.
CAS# 504-24-5 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 3/01/1994 Revision #7 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

Back to product information.

neuromuscular blocking agents such as atracurium and ecuronium.[1] It was suggested that because of its shorter duration of action and lesser effect on the vagus, edrophonium might be the more suitable agent.[2] However, although it has a more rapid onset of action[3,4] than neostigmine and does not to re-induce blockade on repeated administration[5] its ism is not adequately and reliably sustained especially wing profound block[6,7] and some workers consider hat neostigmine is still the agent of choice for use with these gents.[4]

drophonium may be preferable to neostigmine in reversing ntense block due to the short-acting competitive (non-depolarising) agent mivacurium.[9] Neostigmine is reported to inibit plasma cholinesterase which is responsible for the etabolism of mivacurium and the use of neostigmine can herefore delay recovery. Edrophonium appears not to inhibit lasma cholinesterase or reduce mivacurium metabolism. Either agent may be suitable once spontaneous recovery has tarted.[10] However, evaluation of recovery times from mivaurium block comparing edrophonium with spontaneous recovery indicated a small but insignificant advantage in using drophonium.[11] It was considered that spontaneous recovery rom mivacurium may be fast enough not to be influenced significantly by antagonists of neuromuscular blockade.

drophonium is probably the agent of choice for reversal of euromuscular blockade in patients poisoned with anticholinesterase nerve agents who require surgery.[8]

1. Reilly CS, Nimmo WS. New intravenous anaesthetics and neuromuscular blocking drugs: a review of their properties and clinical use. *Drugs* 1987; **34**: 98–135.
2. Hull CJ. New drugs in anaesthesia. *Br J Hosp Med* 1983; **30**: 273–6.
3. Jones RM, *et al.* Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. *Br J Anaesth* 1984; **56**: 453–6.
4. Caldwell JE, *et al.* Antagonism of vecuronium and atracurium: comparison of neostigmine and edrophonium administered at 5% twitch height recovery. *Br J Anaesth* 1987; **59**: 478–81.
5. Astley BA, *et al.* Electrical and mechanical responses after neuromuscular blockade with vecuronium, and subsequent antagonism with neostigmine or edrophonium. *Br J Anaesth* 1987; **59**: 983–8.
6. Caldwell JE, *et al.* Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium: comparison of neostigmine with edrophonium. *Br J Anaesth* 1986; **58**: 1285–9.
7. Mirakhur RK, *et al.* Antagonism of vecuronium-induced neuromuscular blockade with edrophonium or neostigmine. *Br J Anaesth* 1987; **59**: 473–7.
8. Maralliedde L, *et al.* Chemical weapons. *Br Med J* 1991; **302**: 1.
9. Abdulatif M. Recovery characteristics after early administration of anticholinesterases during intense mivacurium-induced neuromuscular block. *Br J Anaesth* 1995; **74**: 20–5.
10. Maddineni VR, *et al.* Recovery of mivacurium block with or without anticholinesterases following administration by continuous infusions. *Anaesthesia* 1994; **49**: 946–8.
11. Connolly FM, *et al.* Antagonism of mivacurium block with edrophonium from various degrees of spontaneous recovery. *Br J Anaesth* 1995; **74**: 229–30.

Snake bite. For the use of anticholinesterases in the treatment of snake-bite, see under Uses and Administration of Neostigmine Methylsulphate, p.1424.

Tetrodotoxin poisoning. Administration of edrophonium intravenously has produced an immediate increase in motor power in patients with respiratory distress and paresis or reduced muscle power following ingestion of puffer fish (*Sphaeroides maculatus* or *Arothron stellatus*).[1] Recovery may be accelerated by subsequent treatment with a long-acting anticholinesterase such as neostigmine. In mild poisoning uncomplicated by respiratory distress or paralysis, neostigmine given alone intramuscularly has produced marked improvement of paraesthesia and numbness.

1. Chew SK, *et al.* Anticholinesterase drugs in the treatment of tetrodotoxin poisoning. *Lancet* 1984; **ii**: 108.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

BP 1993: Edrophonium Injection;
USP 23: Edrophonium Chloride Injection.

Proprietary Preparations

Canad.: Enlon; Tensilon; *Eire:* Tensilon; *S.Afr.:* Tensilon†; *UK:* Camsilon; *USA:* Enlon; Enlon-Plus; Reversol.

Eptastigmine (13786-l)

Eptastigmine *(rINN).*

N-Demethyl-N-heptylphysostigmine. (3aS,8a[illegible]-hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-amate.

$C_{33}N_3O_2 = 359.5$.

CAS — 101246-68-8.

Eptastigmine is a reversible inhibitor of cholinesterase activity; it is a lipophilic derivative of physostigmine (see p.1424). It is being studied in the oral treatment of Alzheimer's disease but has been reported to produce adverse haematological effects.

1. Unni LK, *et al.* Kinetics of cholinesterase inhibition by eptastigmine in man. *Eur J Clin Pharmacol* 1991; **41**: 83–4.
2. Auteri A, *et al.* Pharmacodynamics and pharmacokinetics of eptastigmine in elderly subjects. *Eur J Clin Pharmacol* 1993; **45**: 373–6.

Eseridine Salicylate (4522-m)

Eseridine Salicylate *(rINNM).*

Eserine Aminoxide Salicylate; Eserine Oxide Salicylate; Physostigmine Aminoxide Salicylate; Physostigmine *N*-Oxide Salicylate. (4a*S*,9a*S*)-2,3,4,4a,9,9a-Hexahydro-2,4a,9-trimethyl-1,2-oxazino[6,5-*b*]indol-6-ylmethylcarbamate salicylate.

$C_{15}H_{21}N_3O_3.C_7H_6O_3 = 429.5$.

CAS — 25573-43-7 (eseridine); 5995-96-0 (eseridine salicylate).

Eseridine salicylate is an inhibitor of cholinesterase activity that has been given by mouth in preparations for dyspepsia and other gastric disorders. It has also been studied for use in the treatment of Alzheimer's disease.

A study[1] of the pharmacokinetics of eseridine salicylate following oral administration as oral drops or granules.

1. Astier A, Petitjean O. Pharmacokinetics of an anticholinesterasic agent (eserin N-oxyde) in humans after administration of two galenic forms. *J Pharmacol Clin* 1985; **4**: 521–7.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Fr.: Généséring.

Multi-ingredient preparations. *Fr.:* Vagosérine†.

Fampridine (12364-v)

Fampridine *(USAN, pINN).*

EL-970; Fampridina. 4-Aminopyridine; 4-Pyridinamine.

$C_5H_6N_2 = 94.12$.

CAS — 504-24-5.

Fampridine enhances the release of acetylcholine from nerve terminals and has been used intravenously in some countries to reverse the effects of competitive (non-depolarising) muscle relaxants. It has also been tried by mouth and intravenously in the management of a number of neurological disorders including Eaton-Lambert myasthenic syndrome, multiple sclerosis, and Alzheimer's disease, and for the reversal of neuromuscular blockade in patients with botulism. The overall treatment of these conditions is described on p.1414 (Eaton-Lambert myasthenic syndrome), p.657 (multiple sclerosis), p.1413 (Alzheimer's disease under Dementia), and p.1615 (botulism).

Fampridine has also been considered as a specific antidote in poisoning with calcium-channel blockers such as verapamil.

Adverse effects, especially seizures, may limit its use.

1. Agoston S, *et al.* Antagonism of ketamine-diazepam anaesthesia by 4-aminopyridine in human volunteers. *Br J Anaesth* 1980; **52**: 367–70.
2. Evenhuis J, *et al.* Pharmacokinetics of 4-aminopyridine in human volunteers. *Br J Anaesth* 1981; **53**: 567–9.
3. Ter Wee PM, *et al.* 4-Aminopyridine and haemodialysis in the treatment of verapamil intoxication. *Hum Toxicol* 1985; **4**: 327–9.

Alzheimer's disease. Fampridine enhances acetylcholine release from nerve terminals and has been tried in the treatment of Alzheimer's disease. For a discussion of the management of Alzheimer's disease and other dementias and the various treatments that are being tried, see under Dementia on p.1413. Some references to the use of fampridine in the treatment of Alzheimer's disease are given below.

1. Wesseling H, *et al.* Effects of 4-aminopyridine in elderly patients with Alzheimer's disease. *N Engl J Med* 1984; **310**: 988–9.

Botulism. Fampridine is one of several agents that have been [illegible] to reverse neuromuscular blockade in patients with botulism; see p.1615.

Eaton-Lambert myasthenic syndrome. Agents such as fampridine which increase release of acetylcholine from nerve terminals may be effective in the treatment of Eaton-Lambert myasthenic syndrome, see p.1414. Some references to the use of fampridine are given below.

1. Agoston S, *et al.* Effects of 4-aminopyridine in Eaton Lambert syndrome. *Br J Anaesth* 1978; **50**: 383–5.

Multiple sclerosis. Fampridine has potassium-channel blocking activity and has been tried in the treatment of multiple sclerosis to improve conduction in demyelinated fibres; improvements have been reported in walking, dexterity, and vision, but only small numbers of patients have been studied. For a discussion of the management of multiple sclerosis, including mention of fampridine, see p.657. Some references to the use of fampridine are given below.

1. Davis FA, *et al.* Orally administered 4-aminopyridine improves clinical signs in multiple sclerosis. *Ann Neurol* 1990; **27**: 186–92.
2. Bever CT, *et al.* The effects of 4-aminopyridine in multiple sclerosis patients: results of a randomized, placebo-controlled, double-blind, concentration-controlled, crossover trial. *Neurology* 1994; **44**: 1054–9.

Galantamine Hydrobromide (4517-g)

Galantamine Hydrobromide *(rINNM).*

Galanthamine Hydrobromide; Galanthamini Hydrobromidum. 1,2,3,4,6,7,7a,11c-Octahydro-9-methoxy-2-methylbenzofuro[4,3,2-*ef*g][2]benzazocin-6-ol hydrobromide.

$C_{17}H_{21}NO_3.HBr = 368.3$.

CAS — 357-70-0 (galantamine); 1953-04-4 (galantamine hydrobromide).

Pharmacopoeias. In *Chin.*

The hydrobromide of galantamine, an alkaloid which has been obtained from the Caucasian snowdrop (Voronov's snowdrop), *Galanthus woronowii* (Amaryllidaceae), and related species.

Galantamine hydrobromide is a reversible inhibitor of cholinesterase activity, with actions similar to those of neostigmine (see p.1422). It has been used to curtail the muscle relaxation produced by competitive (non-depolarising) muscle relaxants such as tubocurarine and gallamine.

Galantamine hydrobromide is a long-acting inhibitor of cholinesterase activity which crosses the blood-brain barrier and is being studied in patients with Alzheimer's disease[1] and in mania;[2] for discussions of the management of these disorders, see under Dementia, p.1413 and under Bipolar Disorder, p.300 respectively. Like physostigmine it is reported to reverse opioid-induced respiratory depression without affecting analgesia.[3] The pharmacokinetics of galantamine have been studied.[4,5]

1. Thompsen T, *et al.* Galanthamine hydrobromide in a long-term treatment of Alzheimer's disease. *Dementia* 1990; **1**: 46–51.
2. Snorrason E, Stefansson JG. Galanthamine hydrobromide in mania. *Lancet* 1991; **337**: 557.
3. Weinstock M, *et al.* Effect of physostigmine on morphine-induced postoperative pain and somnolence. *Br J Anaesth* 1982; **54**: 429–34.
4. Westra P, *et al.* Pharmacokinetics of galanthamine (a long-acting anticholinesterase drug) in anaesthetized patients. *Br J Anaesth* 1986; **58**: 1303–7.
5. Bickel U, *et al.* Pharmacokinetics of galanthamine in humans and corresponding cholinesterase inhibition. *Clin Pharmacol Ther* 1991; **50**: 420–8.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Aust.: Nivalin; *Ital.:* Nivalina†.

Guanidine Hydrochloride (12807-c)

Carbamidine Hydrochloride; Iminourea Hydrochloride.

$CH_5N_3.HCl = 95.53$.

CAS — 113-00-8 (guanidine); 50-01-1 (guanidine hydrochloride).

Guanidine hydrochloride enhances the release of acetylcholine from nerve terminals and although it has been given by mouth to reverse neuromuscular blockade in patients with botulism, its efficacy has not been established. Guanidine hydrochloride has also been tried in Eaton-Lambert myasthenic syndrome and other neurological disorders, but its use has been associated with bone-marrow suppression in some patients.

Botulism. Some references to the use of guanidine to reverse neuromuscular blockade in patients with botulism are given

† The symbol † denotes a preparation no longer actively marketed

References: P. van Amerongen, *Curr. med. Res. Opinion*, 1979, *6*, 93; C. Vauterin and M. Bazot, *ibid.*, 101; S. Bornstein, *ibid.*, 107.

Proprietary Names
Survector *(Euthérapie, Fr.)*.

12359-p

Aminobutyric Acid. Gamma-aminobutyric Acid; GABA. 4-Aminobutyric acid.
$C_4H_9NO_2$=103.1.

CAS — 56-12-2.

White crystals with a bitter taste. Freely **soluble** in water; slightly soluble in hot alcohol; practically insoluble in other organic solvents.

Aminobutyric acid is believed to act as an inhibitory neurotransmitter in the CNS. It has been claimed to be of value in cerebral disorders and coma and to have an antihypertensive effect. Adverse effects have included gastro-intestinal disorders, insomnia, headache, and pyrexia.

Over a period of 2 months 7 patients with Huntington's chorea were treated with aminobutyric acid starting at a dose of 1 g and increasing to 12 to 32 g daily. Two patients gained improvement of function and a decrease in choreiform movements and a third patient showed moderate improvement.— R. Fisher *et al.* (letter), *Lancet*, 1974, *1*, 506.

Severe peripheral vascular collapse occurred in one of the authors 90 minutes after taking 8 g of chromatographically pure aminobutyric acid.— T. L. Perry *et al.* (letter), *Lancet*, 1974, *1*, 995. Doses of 1 to 2 g daily and 40 g given over 48 hours had produced no serious side-effects.— R. Fisher *et al.* (letter), *ibid.*, 1347.

γ-Vinyl aminobutyric acid, an irreversible inhibitor of aminobutyric acid transaminase, had a beneficial effect in 7 of 9 patients with tardive dyskinesia when given by mouth in doses ranging from 2 to 6 g daily. Dyskinesia was aggravated in the other 2 patients. Sedation was the most prominent side-effect.— G. P. Tell *et al.* (letter), *New Engl. J. Med.*, 1981, *305*, 581. See also J. Grove *et al.* (letter), *Lancet*, 1980, *2*, 647.

Proprietary Names
Gamarex *(Causyth, Ital.)*; Gammalon *(Daiichi, Jap.)*; Mielogen *(Made, Spain)*.

12360-n

Aminohydroxybutyric Acid. 4-Amino-3-hydroxybutyric acid.
$C_4H_9NO_3$=119.1.

CAS — 352-21-6.

Odourless white crystals or crystalline powder with a slight characteristic taste. Very **soluble** in water; very slightly soluble in alcohol, chloroform, and other organic solvents.

Aminohydroxybutyric acid has been claimed to be of value in neurological disorders and to have an antihypertensive effect. Adverse effects have included dizziness and anorexia.

Proprietary Names
Aminoxan *(Kaken, Jap.)*; Bogil *(Llorente, Spain)*; Gabimex *(Gramon, Arg.)*; Gabob *(Jap.)*; Gamibetal *(ISF, Ital.; Ono, Jap.; Ibsa, Switz.)*; Gabomade *(Made, Spain)*; Gaboril *(Seber, Spain)*.

12361-h

Aminomethiazole Tartrate. 2-Amino-4-methylthiazole hydrogen tartrate.
$C_4H_6N_2S,C_4H_6O_6$=264.3.

Aminomethiazole tartrate is an antithyroid agent.

Proprietary Names
Normotiroide *(Vita, Ital.)*.

12362-m

Aminonitrothiazole *(B. Vet. C. 1965)*. Aminonitrothiazolum. 2-Amino-5-nitrothiazole.
$C_3H_3N_3O_2S$=145.1.

CAS — 1320-42-9.

Pharmacopoeias. In *Nord.*

A greenish-yellow to orange-yellow light odourless powder with a slightly bitter taste. Slightly **soluble** in water; soluble 1 in 250 of alcohol and of ether; practically insoluble in chloroform.

Aminonitrothiazole has been used in veterinary medicine in the prevention and treatment of blackhead (histomoniasis) in turkeys and chickens, and in the treatment of canker (trichomoniasis) in pigeons.

12363-b

Aminopicoline Camsylate. 2-Amino-4-methylpyridine camphor-10-sulphonate.
$C_6H_8N_2,C_{10}H_{16}O_4S$=340.4.

Aminopicoline camsylate has been used for its reputed beneficial effect on the circulation.

Proprietary Names
Piricardio *(Nagel, Ital.)*.

12364-v

4-Aminopyridine.
$C_5H_6N_2$=94.1.

CAS — 504-24-5.

4-Aminopyridine is reported to reverse the effects of non-depolarising muscle relaxants and to have analeptic effects. Improvement of myasthenia gravis has been reported. Aminopyridine hydrochloride and aminopyridine sulphate have been used.

References: W. C. Bowman *et al., J. Pharm. Pharmac.*, 1977, *29*, 616; H. Lundh *et al., J. Neurol. Neurosurg. Psychiat.*, 1977, *40*, 1109; S. Agoston *et al., Br. J. Anaesth.*, 1978, *50*, 383; H. Lundh *et al., J. Neurol. Neurosurg. Psychiat.*, 1979, *42*, 171; S. Agoston *et al., Br. J. Anaesth.*, 1980, *52*, 367; J. Evenhuis *et al., ibid.*, 1981, *53*, 567.

Proprietary Names
Pymadin.

12365-g

Aminorex. Aminoxaphen; McN-742. 2-Amino-5-phenyl-2-oxazoline.
$C_9H_{10}N_2O$=162.2.

CAS — 2207-50-3.

Aminorex is an anorectic agent which was withdrawn from use because of its association with pulmonary hypertension which sometimes proved fatal.

12366-q

Ammonium Benzoate *(B.P.C. 1949)*. Ammonii Benzoas; Ammonium Benzoicum.
$C_6H_5.CO_2NH_4$=139.2.

CAS — 1863-63-4.

White almost odourless scaly crystals. **Soluble** 1 in 6 of water, 1 in 30 of alcohol, and 1 in 8 of glycerol. **Incompatible** with acids, fruit syrups, ferric salts, and alkali hydroxides and carbonates.

Ammonium benzoate has been used for increasing the acidity of the urine and as an expectorant in chronic bronchitis.

12367-p

Ammonium Citrate *(B.P.C. 1949)*. Ammon. Cit.
$C_6H_5O_7(NH_4)_3$=243.2.

CAS — 3458-72-8.

A white or almost white, very deliquescent, crystalline powder with a saline taste. It tends to lose ammonia and to be partly converted to an acid salt. Very **soluble** in water. **Store** in airtight containers.

Ammonium citrate has been used as a mild expectorant and diuretic. After absorption it is converted into carbonate and urea and increases the alkalinity of the urine only slightly.

12368-s

Ammonium Persulphate *(B.P.C. 1934)*.
$(NH_4)_2S_2O_8$=228.2.

CAS — 7727-54-0.

Colourless odourless crystals or white granules or crystalline powder, containing about 7% of available oxygen. **Soluble** 1 in 2 of water; practically insoluble in dehydrated alcohol. It is stable under normal conditions of storage but it decomposes rapidly at about 95°. It decomposes in the presence of moisture and of traces of certain metallic impurities. **Store** in a cool place in airtight containers. Protect from light.

Ammonium persulphate is a powerful oxidising agent which has been used in photography and various industrial processes. Strong solutions are irritant to the skin.

Severe reactions, including loss of consciousness, occurred after using hair bleach containing ammonium persulphate.— C. D. Calnan and S. Shuster, *Arch. Derm.*, 1963, *88*, 812, per *J. Soc. cosmet. Chem.*, 1967, *18*, 681.

12369-w

Ammonium Phosphate *(U.S.N.F., B.P.C. 1949)*. Diammonium Hydrogen Phosphate. Diammonium hydrogen orthophosphate.
$(NH_4)_2HPO_4$=132.1.

CAS — 7783-28-0.

Pharmacopoeias. In *U.S.N.F.*

Colourless crystals or granules with a slight odour and a saline taste. Loses ammonia on exposure to air, forming some ammonium dihydrogen orthophosphate, $NH_4H_2PO_4$. **Soluble** 1 in 2 of water; practically insoluble in alcohol. A 1% solution in water has a pH of 7.6 to 8.2. A 1.76% solution is iso-osmotic with serum. **Incompatible** with alkalis, ferric salts, and salts of heavy metals. **Store** in airtight containers.

Ammonium phosphate was formerly used as a diuretic. It may be used as a buffering agent in pharmaceutical preparations.

12370-m

Ammonium Salicylate.
$C_7H_9NO_3$=155.2.

CAS — 528-94-9.

Ammonium salicylate has been used topically in skin disorders.

Proprietary Names
Salicyl-Vasogen *(Pearson, Ger.)*.

12371-b

Amoscanate. GO-9333; C-9333-Go/CGP-4540. 4-*p*-Nitroanilinophenyl isothiocyanate.
$C_{13}H_9N_3O_2S$=271.3.

CAS — 26328-53-0.

A tasteless yellow substance. M.p. 204° to 206°. Practically **insoluble** in water.

Amoscanate is an anthelmintic structurally related to bitoscanate (see p.89). It is effective against hookworm, *Ancylostoma duodenale* and *Necator americanus*, and against *Schistosoma mansoni* and *S. japonicum*; it has limited effect against *S. haematobium*.
Adverse effects reported include gastro-intestinal effects, skin rash, and giddiness.
References: B. J. Vakil *et al., Trans. R. Soc. trop. Hyg.*, 1977, *71*, 247; B. V. Ashok *et al., Br. J. Pharmac.*, 1977, *4*, 463; J. C. Doshi *et al., Am. J. Med. Hyg.*, 1977, *26*, 636; P. S. Gupta *et al., J. Med. Hyg.*, 1979, *82*, 117, per *Trop. Dis. Bull.*, 1980, *77*, 391; Tech. Rep. Ser. Wld Hlth Org. No. 643, 1980.

<1>
Authors
Segal JL. Brunnemann SR.
Title
4-Aminopyridine improves **pulmonary function in quadriplegic humans** with longstanding spinal cord injury.
Source
Pharmacotherapy. 17(3):415-23, 1997 May-Jun.
Abstract
STUDY OBJECTIVE: To test the hypothesis that 4-aminopyridine (4-AP) might cause clinically evident improvement in pulmonary function in humans with chronic spinal cord injury (chronic SCI). DESIGN: Balanced, open-label study with subjects consecutively enrolled. SETTING: Spinal Cord Injury Service, university-affiliated tertiary level care Department of Veterans Affairs Medical Center. PATIENTS: Seventeen healthy men and women suffering from traumatic SCI (11 quadriplegic, 6 paraplegic patients) for more than 1 year. INTERVENTIONS: Each subject was given a **single dose of 4-AP 10 mg orally in an immediate-release formulation**. MEASUREMENTS AND MAIN RESULTS: Significant increases in mean values of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), maximal inspiratory pressure (MIP), and **maximal expiratory pressure** (MEP) **that persisted for at least 12 hours** were **demonstrated in quadriplegic patients beginning 6 hours after 4-AP administration**. Tests of pulmonary function that demonstrated statistically significant increases at any time were also numerically, if not statistically, increased at 24 hours compared with pretreatment values obtained in 4-AP-naive subjects. CONCLUSIONS: The administration of a single dose of an immediate-release **formulation of 4-AP** to **humans with longstanding, traumatic quadriplegia is associated with sustained, clinically meaningful, and statistically significant improvements in pulmonary function**. We suggest that the administration of 4-AP may have a salutary effect in patients suffering from SCI and appears to be associated with potentially clinically significant reductions in the pathophysiologic pulmonary sequelae of SCI.

<4>
Authors
Schwid SR. Petrie MD. McDermott MP. Tierney DS. Mason DH. Goodman AD.
Title
Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple

sclerosis.
Source
Neurology. 48(4):817-21, 1997 Apr.
Abstract
OBJECTIVE: To evaluate the efficacy of 4-aminopyridine sustained release (4AP SR) (fampridine, EL-970) using quantitative measures of motor function in multiple sclerosis (MS) patients. BACKGROUND: In vitro, 4AP improves conduction through demyelinated axons. A previous multicenter trial of 4AP SR using the Expanded Disability Status Scale (EDSS) as the primary outcome was unable to establish clinical efficacy. DESIGN/METHODS: Ten MS patients with stable motor deficits (EDSS 6.0-7.5) were given 4AP SR 17.5 mg bid and placebo for 1 week each in a double-blind, placebo-controlled, crossover trial. Time to walk 8 meters, time to climb four stairs, maximum voluntary isometric contraction measured quantitatively (MVICT), manual muscle testing (MMT), grip strength, EDSS, and the patient's global impression were measured. RESULTS: **Timed gait was improved on 4AP SR compared with placebo in 9 of 10 subjects (p = 0.02)**. Timed stair climbing, MVICT, MMT, grip strength, and EDSS showed nonsignificant improvements on 4AP SR. Based on their global impressions, seven subjects preferred 4AP SR over placebo; only one preferred placebo. There were no serious side effects. CONCLUSION: **4AP SR improved motor function in MS patients**. The quantitative outcomes used in this study permit more sensitive evaluation of the therapeutic effect and promise to be useful in future trials of symptomatic treatments for MS.

<5>
Authors
Chang FC. Bauer RM. Benton BJ. Keller SA. Capacio BR.
Title
4-Aminopyridine antagonizes saxitoxin-and tetrodotoxin-induced cardiorespiratory depression.
Source
Toxicon. 34(6):671-90, 1996 Jun.
Abstract
Antagonism of saxitoxin-and tetrodotoxin-induced lethality by 4-aminopyridine was studied in urethane-anesthetized guinea pigs instrumented for the concurrent recordings of medullary respiratory-related unit activities (Botzinger complex and Nu. para-Ambiguus), diaphragmatic electromyogram, electrocorticogram, Lead II electrocardiogram, blood pressure, end-tidal CO2 and arterial O2/CO2/pH. The toxin (either saxitoxin or

tetrodotoxin) was infused at a dose rate of 0.3 microgram/kg/min (i.v.) to produce a state of progressive cardiorespiratory depression. The animals were artificially ventilated when the magnitude of integrated diaphragm activities was reduced to 50% of control. Immediately after the disappearance of the diaphragm electromyogram, the toxin infusion was terminated, and 4-aminopyridine (2 mg/kg, i.v.) was administered. The therapeutic effect of 4-aminopyridine was striking in that the toxin-induced blockade of diaphragmatic neurotransmission, vascular hypotension, myocardial anomalies, bradycardia and aberrant discharge patterns of medullary respiratory-related neurons could all be promptly restored to a level comparable to that of control condition. The animals were typically able to breathe spontaneously within minutes after 4-aminopyridine. **At the dose level used to achieve the desired therapeutic responses, 4-aminopyridine produced no sign of seizure and convulsion.** Although less serious side-effects such as cortical excitant/arousal and transient periods of fascicular twitch could be observed, these events were of minor concern, in our opinion, particularly in view of the remarkable therapeutic effects of 4-aminopyridine.

<8>
Authors
Chen HM. Lin CH. Wang TM.
Title
Effects of 4-aminopyridine on saxitoxin intoxication.
Source
Toxicology & Applied Pharmacology. 141(1):44-8, 1996 Nov.
Abstract
Effects of 4-aminopyridine (4-AP) on neurotoxicity induced by saxitoxin (STX) are investigated in this study. In vitro, twitch tension evoked by nerve stimulation was depressed by STX (1.35 nM) in rat phrenic nerve-diaphragm preparations, and this inhibition was antagonized by 4-AP (0.1 mM). **In addition, 4-AP (0.1 mM) restored the firing of membrane action potentials that were suppressed or even abolished by 0.334 nM STX in frog sartorius muscles.** In vivo studies showed that 4-AP (0.3 mg/kg, iv) significantly reversed the respiratory rate, tidal volume, and blood pressure to normal values in anesthetized STX-toxicosis rats. **Furthermore, 4-AP (0.75-6 mg/kg, ip) not only prolonged the survival time but also decreased the mortality of mice (71-43%) at a normally lethal dose (30 micrograms/kg, ip) of STX. The results suggest that 4-AP may be useful as an antidote for STX intoxication.**

<11>
Authors
Perez-Espejo MA. Haghighi SS. Adelstein EH. Madsen R.
Title
The effects of taxol, methylprednisolone, and 4-aminopyridine in compressive spinal cord injury: a qualitative experimental study.
Source
Surgical Neurology. 46(4):350-7, 1996 Oct.
Abstract
BACKGROUND: Taxol is a diterpene alkaloid that stimulates tubulin production in cells. It may be effective in preserving the cytoskeleton of spinal cord axons after injury. METHODS: Thirty-nine rats were submitted to spinal cord compression. The animals were divided into three groups that received taxol (18.75 mg/m2), methylprednisolone (30 mg/kg), or 4-aminopyridine (1 mg/kg). Taxol was administered as one dose immediately after injury and two additional doses on days 14 and 21. Methylprednisolone was given as a single injection immediately postinjury. Four-aminopyridine was administered on days 25, 26, and 27. A group of nine injured animals served as a control without any treatment. Evoked potentials were recorded before, during, and 4 weeks postinjury. Behavioral tests were measured to evaluate recovery of motor function. RESULTS: The taxol and methylprednisolone-treated animals demonstrated a significant improvement in comparison with the control group. No functional improvement was found at 1 mg/kg treatment of 4-aminopyridine in rats. CONCLUSIONS: We conclude that taxol and methylprednisolone given shortly after the compression injury improve functional outcome after an incomplete spinal cord injury.

<12>
Authors
Wananukul W. Keyler DE. Pentel PR.
Title
Effect of calcium chloride and 4-aminopyridine therapy on desipramine toxicity in rats.
Source
Journal of Toxicology - Clinical Toxicology. 34(5):499-506, 1996.
Abstract
BACKGROUND: Hypotension is a major contributor to mortality in tricyclic antidepressant overdose. Recent data suggest

that tricyclic antidepressants inhibit calcium influx in some tissues. This study addressed the potential role of calcium channel blockade in tricyclic antidepressant-induced hypotension. METHODS: Two interventions were studied that have been shown previously to improve blood pressure with calcium channel blocker overdose. CaCl2 and 4-aminopyridine. Anesthetized rats received the tricyclic antidepressant desipramine IP to produce hypotension, QRS prolongation, and bradycardia. Fifteen min later, animals received CaCl2, NaHCO3, or saline. In a second experiment, rats received tricyclic antidepressant desipramine IP followed in 15 min by 4-aminopyridine or saline. RESULTS: NaHCO3 briefly (5 min) reversed hypotension and QRS prolongation. CaCl2 and 4-aminopyridine failed to improve blood pressure. The incidence of ventricular arrhythmias ($p = 0.004$) and seizures ($p = 0.03$) in the CaCl2 group was higher than the other groups. CONCLUSION: **The administration of CaCl2 or 4-aminopyridine did not reverse tricyclic antidepressant-induced hypotension** in rats. CaCl2 therapy **may possibly** worsen both cardiovascular and central nervous system toxicity. These findings **[redacted] support** a role for calcium channel inhibition in the pathogenesis of tricyclic antidepressant-induced hypotension.

<15>
Authors
Pickett TA. Enns R.
Title
Atypical presentation of 4-aminopyridine overdose.
Source
Annals of Emergency Medicine. 27(3):382-5, 1996 Mar.
Abstract
4-Aminopyridine (4-AP) is an investigational drug for the treatment of neurologic disorders including **multiple** sclerosis (MS). Until recently, relatively little was known about 4-AP toxicity in overdose; the only recorded cases involved neurologic symptoms ranging from mild parasthesias to tonic-clonic seizures. We report a case of accidental 4-AP overdose that resulted in continuous, dystonic, choreoathetoid-type movements that responded to treatment with standard anticonvulsant dosages of benzodiazepines.

<17>
Authors
Haghighi SS. Pugh SL. Perez-Espejo MA. Oro JJ.
Title

Effect of 4-aminopyridine in acute spinal cord injury.
Source
Surgical Neurology. 43(5):443-7, 1995 May.
Abstract
BACKGROUND: The demyelination process has been proven to be an important factor contributing to long-term sensory and motor impairments after spinal cord injury (SCI). The loss of myelin promotes exposure of K+ channels in internodal region of the damaged myelinated axons leading to K+ efflux into the neurons with subsequent blockage of action potentials. The potassium channel blocker 4-aminopyridine (4-AP) has been effective in restoring some sensory and motor impairment in incomplete SCI patients. The effect of this compound given immediately after an acute injury is not known. The objective of this study was to determine if blockage of K+ ions efflux immediately after an acute SCI would improve neuronal conduction in this model of injury. METHODS: Cortical somatosensory evoked potentials (SSEPs) were recorded before and after a weight-induced compression injury of 120 grams, and were monitored up to 5 hours postinjury. A randomized treatment was initiated with administration of either vehicle or 4-AP. All 4-AP treatments were given as intravenous bolus injections of 1.0, 0.5, and 0.3 mg/kg at 1, 2, and 3 hours after the trauma. RESULTS: The SSEPs were abolished immediately after the injury in all control and treated animals. Both groups showed spontaneous recovery of the SSEPs at the rate of 44.5% for the 4-AP treated and nontreated groups at the second hour postinjury. This recovery rate remained the same for both groups at the end of the experiments. CONCLUSIONS: Based on the recovery of the SSEPs, our data indicate that early administration of 4-AP [redacted] any beneficial effect on axonal function during acute stage of spinal cord injury.

<26>
Authors
Hayes KC. Potter PJ. Wolfe DL. Hsieh JT. Delaney GA. Blight AR.
Title
4-Aminopyridine-sensitive neurologic deficits in patients with spinal cord injury.
Source
Journal of Neurotrauma. 11(4):433-46, 1994 Aug.
Abstract
4-Aminopyridine (4-AP) is a potassium channel blocking agent with the ability to restore conduction in demyelinated internodes of axons of the spinal cord. The

present investigation sought to obtain electrophysiologic evidence of the effect of 4-AP in ameliorating central conduction deficits in a group of patients (n = 6) with spinal cord injury (SCI). The group was selected on the basis of having temperature-dependent central conduction deficits. 4-AP (24-25 mg total dose) was delivered intravenously at 6 mgh-1 or 15 mgh-1 while somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs) were recorded as indices of central conduction. Two patients exhibited marked increases in the amplitude of cortical SEPs, and in one of these, 4-AP brought about a reduced central conduction time from L1 to cortex. Four patients revealed increased amplitude MEPs with concomitant reduction in latency indicative of enhanced conduction in corticospinal or corticobulbospinal pathways. Two of these patients demonstrated increased voluntary motor unit recruitment following 4-AP. Clinical examination revealed reduced spasticity (n = 2), reduced pain (n = 1), increased sensation (n = 1), improved leg movement (n = 3), and restored voluntary control of bowel (n = 1). These results support the hypothesis that 4-AP induces neurologic benefits in some patients with SCI. They are also consistent with the emerging concept that pharmaceutical amelioration of central conduction deficits caused by focal demyelination may contribute to the management of a select group of patients with compressive or contusive SCI.

<27>
Authors
Li L. Zhang YP.
Title
[Therapy of experimental autoimmune myasthenia gravis in rabbits with 4-aminopyridine and 3,4-diaminopyridine]. [Chinese]
Source
Chung-Kuo Yao Li Hsueh Pao - Acta Pharmacologica Sinica. 15(4):358-62, 1994 Jul.
Abstract
The autoimmune myasthenia gravis (AMG) in rabbits was produced by intradermal injection of N-AChR-rich membrane vesicles isolated from the electric organ of Narcine limlei. After i.v. 4-aminopyridine (4-AP) 0.8 mg.kg-1 to 8 AMG rabbits, their general posture improved promptly, the features of gastrocnemius compound action potentials and toe twitches elicited by 4-Hz stimuli applied to the sciatic nerve returned to normal, and the tetanic plateau evoked by 50-Hz indirect stimulation was again well sustained. This improved condition lasted 9.1 +/- 2.5 h.

Other 8 AMG rabbits given 3,4-diaminopyridine (3,4-DAP) 0.4 mg.kg-1 showed a similar improvement for 9.3 +/- 3.1 h. These results indicated that 4-AP and 3,4-DAP were effective in treating the AMG in rabbits, they may be useful in the clinical treatment of myasthenia gravis patients.

<29>
Authors
Polman CH. Bertelsmann FW. de Waal R. van Diemen HA. Uitdehaag BM. van Loenen AC. Koetsier JC.
Title
4-Aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis.
Source
Archives of Neurology. 51(11):1136-9, 1994 Nov.
Abstract
OBJECTIVE: To compare the efficacy and toxicity of 4-aminopyridine and 3,4-diaminopyridine in patients with multiple sclerosis. DESIGN: Intervention study with a before-after design and a randomized, double-blind, crossover design. SETTING: University referral center. PATIENTS: Twenty-four patients with definite multiple sclerosis who had been treated in a previous clinical trial with 4-aminopyridine. INTERVENTIONS: Nonresponders to treatment with 4-aminopyridine (14 patients) were treated with 3,4-diaminopyridine in a 4-week, open-label trial with doses up to 1.0 mg/kg of body weight (before-after design). Responders to treatment with 4-aminopyridine (10 patients) participated in a comparative study of 6 weeks' duration with 4-aminopyridine and 3,4-diaminopyridine according to a randomized, double-blind, double-crossover design. MAIN OUTCOME MEASURES: Neurophysiologic variables for nonresponders, neurologic functions and symptoms on a visual analogue scale for responders, and side effects for both groups. RESULTS: Toxicity profiles of 4-aminopyridine and 3,4-diaminopyridine were different, and systemic tolerability was reduced for 3,4-diaminopyridine. 4-Aminopyridine was more effective than 3,4-diaminopyridine, especially for ambulation, fatigue, and overall daily functioning. CONCLUSION: Our data suggest that, concerning both efficacy and side effects, 4-aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis.

<30>
Authors

Smits RC. Emmen HH. Bertelsmann FW. Kulig BM. van Loenen AC. Polman CH.

Title

The effects of 4-aminopyridine on cognitive function in patients with multiple sclerosis: a pilot study.

Source

Neurology. 44(9):1701-5, 1994 Sep.

Abstract

4-Aminopyridine (4-AP) has a favorable effect on the disability of certain patients with MS. We investigated the effect of 4-AP on neuropsychological performance in 20 MS patients using a randomized, double-blind, placebo-controlled, crossover design. Although there was a trend for improved performance with 4-AP for two of the tests, we could not demonstrate significant effects of 4-AP on cognitive function.

<32>

Authors

Bever CT Jr.

Title

The current status of studies of aminopyridines in patients with multiple sclerosis. [Review] [29 refs]

Source

Annals of Neurology. 36 Suppl:S118-21, 1994.

Abstract

Because the symptomatic treatments for multiple sclerosis (MS) are limited, new approaches have been sought. Anatomical studies of MS lesions show a relative preservation of axons, and clinical studies suggest that some of the neurological impairment in patients with MS is physiological. Electrophysiological studies suggest that demyelination exposes axonal potassium channels that decrease action-potential duration and amplitude, hindering action-potential propagation. Potassium channel blockers, including aminopyridines, have been shown to improve nerve conduction in experimentally demyelinated nerves. Two potassium channel blockers, 4-aminopyridine (AP) and 3,4 diaminopyridine (DAP) have been tested in patients with MS. Preliminary studies of AP demonstrated benefit in many temperature-sensitive patients with MS, and improvement of function was found in a large randomized double-blind, placebo-controlled crossover trial of 3 months of oral treatment in 68 patients with MS. An open-label trial of DAP showed improvement in some deficits, and a double-blind placebo-controlled trial showed significant improvements in prospectively defined neurological deficits. A crossover comparison of the two agents suggested that AP produces

more central nervous system side effects (dizziness and confusion), whereas DAP produces more peripheral side effects (paresthesias and abdominal pain). Both agents have rarely caused seizures. These studies suggest that aminopyridines may provide a new approach to the symptomatic treatment of MS. [References: 29]

<33>

Authors

Bever CT Jr. Young D. Anderson PA. Krumholz A. Conway K. Leslie J. Eddington N. Plaisance KI. Panitch HS. Dhib-Jalbut S. et al.

Title

The effects of 4-aminopyridine in multiple sclerosis patients: results of a randomized, placebo-controlled, double-blind, concentration-controlled, crossover trial.

Source

Neurology. 44(6):1054-9, 1994 Jun.

Abstract

Because **4-aminopyridine (AP) improves residual deficits** in **some multiple sclerosis (MS) patients but has a narrow toxic-to-therapeutic margin**, we compared the safety and efficacy of two target peak serum concentration ranges (low: 30 to 59 ng/ml and high: 60 to 100 ng/ml). We enrolled eight MS patients with temperature-sensitive visual and motor deficits in a randomized, placebo-controlled, double-blind, crossover trial of short-term oral AP treatment. We randomized patients to a sequence of three treatments on three separate days: placebo, low serum concentration, and high serum concentration. We determined dosing to achieve the desired steady-state peak serum concentration ranges from a test dose and population pharmacokinetic parameters using bayesian estimation. Contrast sensitivity, standard neurologic examination, ratings of videotaped neurologic examinations, and quantitative strength assessment all improved with treatment, but flicker fusion frequency, visual evoked response latencies, and Expanded Disability Status Scale scores did not. **All patients experienced side effects during the high-serum-concentration arm.** A grand mal seizure occurred at a serum AP level of 104 ng/ml, and an acute confusional episode occurred at 114 ng/ml. AP treatment produced improvements in residual deficits in MS patients, but the occurrence of significant toxicity suggests that AP serum levels should be monitored and peak levels above 100 ng/ml should be avoided. Concentration-control methodology may be useful in testing putative treatments for other neurologic diseases.

<36>
Authors
Polman CH. Bertelsmann FW. van Loenen AC. Koetsier JC.
Title
4-aminopyridine in the treatment of patients with multiple sclerosis. Long-term efficacy and safety.
Source
Archives of Neurology. 51(3):292-6, 1994 Mar.
Abstract
OBJECTIVE: To study the long-term efficacy and safety of 4-aminopyridine in patients with multiple sclerosis. DESIGN: Case series, follow-up varying from 6 to 32 months. SETTING: University referral center. PATIENTS: Thirty-one patients with definite MS, 23 of them being exposed to long-term administration (6 to 32 months) of 4-aminopyridine, since they showed a favorable initial response to the drug. INTERVENTIONS: Long-term oral treatment with 4-aminopyridine in daily doses of up to 0.5 mg/kg of body weight. MAIN OUTCOME MEASURES: Neurologic functions and symptoms as reported by the patients; side effects. RESULTS: Twenty of 23 patients who showed a favorable initial response benefited from long-term administration. **Ambulation and fatigue (each in 13 patients) and visual function (in five patients) were most frequently reported to be improved.** Three major side effects did occur during a follow-up of 406 patient months: a generalized epileptic seizure in two patients and hepatitis in one. CONCLUSIONS: Although a substantial proportion of patients with multiple sclerosis seem to benefit from long-term administration of 4-aminopyridine, additional studies are needed to clarify the exact value of the drug.

<40>
Authors
van Diemen HA. Polman CH. van Dongen MM. Nauta JJ. Strijers RL. van Loenen AC. Bertelsmann FW. Koetsier JC.
Title
4-Aminopyridine induces functional improvement in multiple sclerosis patients: a neurophysiological study.
Source
Journal of the Neurological Sciences. 116(2):220-6, 1993 Jun.
Abstract
This study reports on the neurophysiological measurements that were performed in the context of a randomized,

double-blind, placebo-controlled, cross-over study with intravenously administered 4-aminopyridine (4-AP) in 70 patients with definite multiple sclerosis (MS). A beneficial effect of 4-AP was found for both visual evoked response and eye movement registration parameters. This study extends the experimental data obtained on animal nerve fibers, showing that 4-AP can improve impulse conduction in demyelinated nerve, to clinical data which indicate that 4-AP induces an objective improvement in the central nervous system function in MS-patients. It thereby also provides a theoretical basis for clinical efficacy of 4-AP in MS.

<42>
Authors
Hansebout RR. Blight AR. Fawcett S. Reddy K.
Title
4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients [see comments].
Source
Journal of Neurotrauma. 10(1):1-18, 1993 Spring.
Abstract
The potassium channel blocking drug 4-aminopyridine (4-AP) was administered to eight patients with chronic spinal cord injury, in a therapeutic trial based on the ability of the drug to restore conduction of impulses in demyelinated nerve fibers. The study was performed using a randomized, double-blind, crossover design, so that each patient received the drug and a vehicle placebo on different occasions, separated by 2 weeks. Drug and placebo were delivered by infusion over 2 h. An escalating total dose from 18.0 to 33.5 mg was used over the course of the study. Subjects were evaluated neurologically before and after the infusion. Two subjects returned for a second trial after 4 months and were examined daily for 3 to 4 days following drug infusion. Side effects were consistent with previous reports. Administration of the drug was associated with significant temporary neurologic improvement in five of six patients with incomplete spinal cord injury. No effect was detected in two cases of complete paraplegia and one of two severe incomplete cases (Frankel class B). Improvements in neurologic status following drug administration included increased motor control and sensory ability below the injury, and reduction in chronic pain and spasticity. The effects persisted up to 48 h after infusion of the drug, and patients largely returned to preinfusion status by 3 days. Compared with the more rapid elimination of the drug,

these prolonged neurologic effects appear to involve a secondary response and are probably not a direct expression of potassium channel blockade.

<43>
Authors
Hayes KC. Blight AR. Potter PJ. Allatt RD. Hsieh JT. Wolfe DL. Lam S. Hamilton JT.
Title
Preclinical trial of 4-aminopyridine in patients with chronic spinal cord injury.
Source
Paraplegia. 31(4):216-24, 1993 Apr.
Abstract
4-Aminopyridine (4-AP) is a K+ channel blocking agent that enhances nerve conduction through areas of demyelination by prolonging the duration of the action potential and increasing the safety factor for conduction. We have investigated the effects of 4-AP (24 mg total dose-intravenous) in 6 patients with spinal cord injury (3 complete, 3 incomplete) with the intent of overcoming central conduction block, or slowing, due to demyelination. Vital signs remained stable and only mild side effects were noted. The 3 patients with incomplete injuries all demonstrated enhanced volitional EMG interference patterns and one patient exhibited restored toe movements. The changes were reversed on drug washout. There were no changes in segmental reflex activities. These results are consistent with those obtained from 4-AP trials with animal models of spinal cord injury, showing modest therapeutic benefit attributable to enhanced central conduction.

<44>
Authors
van Diemen HA. van Dongen MM. Dammers JW. Polman CH.
Title
Increased visual impairment after exercise (Uhthoff's phenomenon) in multiple sclerosis: therapeutic possibilities.
Source
European Neurology. 32(4):231-4, 1992.
Abstract
The Uhthoff symptom, a transient impairment of visual function after exercise, is demonstrated in 2 multiple sclerosis patients. Following exercise, impairment of visual function, as documented most clearly by the testing of contrast sensitivity, was less obvious after body

surface cooling and after treatment with orally administered 4-aminopyridine. It is hypothesized that both treatment modalities improve the nerve conduction safety factor and thereby prevent the occurrence of a conduction block, which is believed to be the mechanism underlying the Uhthoff symptom.

<47>
Authors
van Diemen HA. Polman CH. van Dongen TM. van Loenen AC. Nauta JJ. Taphoorn MJ. van Walbeek HK. Koetsier JC.
Title
The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study.
Source
Annals of Neurology. 32(2):123-30, 1992 Aug.
Abstract
To find out whether treatment with 4-aminopyridine is beneficial in multiple sclerosis (MS), 70 patients with definite MS entered into a randomized, double-blind, placebo-controlled, cross-over trial in which they were treated with 4-aminopyridine and placebo for 12 weeks each **(maximum dose, 0.5 mg/kg of body weight)**. The estimated **effect of the treatment** as measured with the Kurtzke expanded disability status scale, which was the main evaluation parameter, was 0.28 point ($p = 0.001$). A significant decrease in the scale score (1.0 point or more) was encountered in 10 patients (16.4%) during oral treatment with 4-aminopyridine whereas it was not seen during placebo treatment (p less than 0.05). A significant subjective improvement (defined as an improvement that significantly affected the activities of normal daily life) was indicated by 18 patients (29.5%) during 4-aminopyridine treatment and by 1 patient (1.6%) during placebo treatment (p less than 0.05). Significant improvements related to 4-aminopyridine occurred in a number of neurophysiological parameters. **No serious side effects were encountered. However, subjective side effects such as paresthesias, dizziness, and light-headedness were frequently reported during 4-aminopyridine treatment.** Analysis of subgroups revealed that there was no difference in efficacy between those patients randomized to receive 4-aminopyridine and then placebo and those randomized to receive placebo and then 4-aminopyridine or between patients with and those without subjective side effects. Especially patients with temperature-sensitive symptoms and patients characterized by having a longer duration of the disease and being in a

progressive phase of the disease were likely to show clear clinical benefit.

<48>
Authors
Nockels R. Young W.
Title
Pharmacologic strategies in the treatment of experimental spinal cord injury. [Review] [127 refs]
Source
Journal of Neurotrauma. 9 Suppl 1:S211-7, 1992 Mar.
Abstract
Remarkable advances have been made in pharmacologic treatments of acute and chronic spinal cord injury. The recent National Acute Spinal Cord Injury Study (NASCIS) showed that very high dose methylprednisolone given within 8 hr after injury improves neurologic recovery. The mechanism is believed to be inhibition of lipid peroxidation. Many other drugs have been claimed to be beneficial in animal studies, including other lipid peroxidation inhibitors, free radical scavengers, opiate receptor blockers, NMDA receptor blockers, calcium channel blockers, inhibitors of arachidonic acid metabolism, and protease inhibitors. In chronic spinal cord injury, much progress also has been made. Myelin was found to possess factors that inhibit axonal regeneration. Blocking these factors enhances spinal cord regeneration. Monosialic gangliosides (GM1) were recently found to improve neurologic recovery in spinal-cord-injured patients. Given as late as 48-72 hr after injury, the mechanism of action is not well understood. However, the GM1 results give hope that recovery mechanisms can be manipulated pharmacologically. Nonregenerative therapy for chronic spinal cord injury is also being developed. Several drugs, including 4-aminopyridine and baclofen, respectively blockers of potassium channels and GABA-B receptors, improve conduction in demyelinated axons. These drugs may be useful for identifying patients who might benefit from remyelination therapy. Finally, NASCIS has complicated acute spinal cord injury studies. To bring a drug to clinical trial, an investigator must now determine the optimal treatment dose, timing, and duration over a range of injury severities, in comparison and combination with methylprednisolone. This requirement has so increased the scale of drug testing that multicenter laboratory trials may be necessary. [References: 127]

<50>
Authors
Stefoski D. Davis FA. Fitzsimmons WE. Luskin SS. Rush J. Parkhurst GW.
Title
4-Aminopyridine in multiple sclerosis: prolonged administration.
Source
Neurology. 41(9):1344-8, 1991 Sep.
Abstract
In an earlier study, we demonstrated efficacy of single oral doses of 4-aminopyridine (4-AP) in improving motor and visual signs in multiple sclerosis (MS) patients for a mean of 4.97 hours. We attempted to determine whether efficacy could safely be prolonged using multiple daily doses over several days by administering 7.5 to 52.5 mg 4-AP to 17 temperature-sensitive MS patients in one to three daily doses at 3- to 4-hour intervals over 1 to 5 days in a double-blind study. Nine of these patients were also tested with identically appearing placebo. Thirteen of the 17 patients (76%) given 4-AP showed clinically important motor and visual improvements compared with three of nine in the placebo group. Average peak improvement scores were 0.40 for 4-AP and 0.12 for placebo. Seventy percent of the daily 4-AP improvements lasted 7 to 10 hours. The improvements for two consecutive doses of 4-AP lasted a mean of 7.07 hours (83% of the average 8.53-hour treatment-observation period) compared with 2.36 hours for placebo (26% of the average 9.06-hour treatment-observation period). No serious side effects occurred. 4-AP is a promising drug for the symptomatic treatment of MS.

<51>
Authors
Blight AR. Toombs JP. Bauer MS. Widmer WR.
Title
The effects of 4-aminopyridine on neurological deficits in chronic cases of traumatic spinal cord injury in dogs: a phase I clinical trial.
Source
Journal of Neurotrauma. 8(2):103-19, 1991 Summer.
Abstract
A Phase I trial of 4-aminopyridine (4-AP) was carried out in 39 dogs referred to the veterinary teaching hospital with naturally occurring traumatic paraplegia or paraparesis. The rationale for the study was provided by the observation that 4-AP restores conduction in demyelinated nerve fibers in experimental spinal cord

injury. Most injuries (77%) resulted from degenerative disk disease, occurring at or near the thoracolumbar junction, and producing chronic, complete paraplegia. Neurological examination of each dog was recorded on videotape before and at intervals after administration of 4-AP. The drug was administered systemically in total doses between 0.5 and 1 mg/kg body weight. Three areas of neurological status changed significantly at 15-45 minutes following administration of 4-AP: (a) striking improvements in hindlimb placing occurred in 18 animals; (b) increased awareness of painful stimuli to the hindlimb in 10 animals; (c) partial recovery of the cutaneus trunci muscle reflex of the back skin in 9 animals. These effects reversed within a few hours of administration. Other animals (36%) showed no change in neurological signs except a slight enhancement of hindlimb reflex tone. Significant side effects were seen in 6 dogs receiving higher intravenous doses, with elevation of body temperature and apparent anxiety, leading to mild seizures in 3 of the animals. These seizures were controlled with diazepam. The results indicate that conduction block may contribute significantly to functional deficits in closed-cord injuries and that potassium channel blockade may prove to be a valid, if limited approach to therapeutic intervention in chronic paraplegia and paraparesis.

<52>
Authors
Wiseman EJ. Jarvik LF.
Title
Potassium channel blockers: could they work in Alzheimer disease?. [Review] [38 refs]
Source
Alzheimer Disease & Associated Disorders. 5(1):25-30, 1991 Spring.
Abstract
Many of the actions of potassium channel blockers, such as 4-aminopyridine, appear to complement the deficits in Alzheimer disease. The two clinical studies in the literature are contradictory, so potassium channel blockers may still merit trial in Alzheimer disease. [References: 38]

<59>
Authors
Davis FA. Stefoski D. Rush J.
Title

Orally administered 4-aminopyridine improves clinical signs in multiple sclerosis [see comments].

Source
Annals of Neurology. 27(2):186-92, 1990 Feb.

Abstract
4-Aminopyridine (4-AP), a potassium channel blocker, restores conduction in blocked, demyelinated animal nerve. Its administration to multiple sclerosis (MS) patients produces transient neurological improvements. Vision improves after either oral or intravenous administration, whereas motor function improvement has been reported only with the latter. To assess further its potential as a practical symptomatic treatment, we studied the efficacy of single, oral doses of 4-AP on both visual and motor signs in MS. Twenty temperature-sensitive male MS patients were given either 10 to 25 mg of 4-AP or identically appearing lactose placebo capsules. Static quantitative perimetry, critical flicker-fusion, visual acuity, visual evoked potentials, and videotaped neurological examinations were monitored. All of 15 MS patients given 4-AP mildly to markedly improved. Motor functions (power, coordination, gait) improved in 9 of 13 involved, vision in 11 of 13, and oculomotor functions in 1 of 2. Improvements developed gradually at doses as low as 10 mg, usually beginning within 60 minutes after drug administration, and reversed gradually over 4 to 7 hours. No serious adverse effects occurred. No significant changes were observed in 5 MS patients given placebo. We conclude that orally administered 4-AP produces clinically important improvements in multiple, chronic deficits in MS. Further studies are warranted to assess efficacy and safety of prolonged administration.

4-Aminopyridine in Multiple Sclerosis

4-aminopyridine (4-AP), a blocker of potassium channels, prolongs the duration of nerve action potentials, and improves conduction in demyelinated axons.

American and European studies over the last 6 years have confirmed its efficacy in the symptomatic treatment of MS related fatigue, muscle weakness, and the heat sensitivity experienced by MS patients. Our Center has treated over 200 patients using short-acting orally administered doses as needed or 3 to 4 times daily. Side effects have been minimal.

This compound is not yet FDA approved for general use, but can be prescribed by our Center.

Contact:
1-713-798-7707

Department of Neurology, Baylor College of Medicine

Comments to: neurons

URL:http://www.bcm.tmc.edu/neurol/index.html

CLINICAL RESEARCH ARTICLES

4-Aminopyridine Improves Pulmonary Function in Quadriplegic Humans with Longstanding Spinal Cord Injury

Jack L. Segal, M.D., FACP, FCP, and Sherry R. Brunnemann, B.S.

Study Objective. To test the hypothesis that 4-aminopyridine (4-AP) might cause clinically evident improvement in pulmonary function in humans with chronic spinal cord injury (chronic SCI).

Design. Balanced, open-label study with subjects consecutively enrolled.

Setting. Spinal Cord Injury Service, university-affiliated tertiary level care Department of Veterans Affairs Medical Center.

Patients. Seventeen healthy men and women suffering from traumatic SCI (11 quadriplegic, 6 paraplegic patients) for more than 1 year.

Interventions. Each subject was given a single dose of 4-AP 10 mg orally in an immediate-release formulation.

Measurements and Main Results. Significant increases in mean values of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) that persisted for at least 12 hours were demonstrated in quadriplegic patients beginning 6 hours after 4-AP administration. Tests of pulmonary function that demonstrated statistically significant increases at any time were also numerically, if not statistically, increased at 24 hours compared with pretreatment values obtained in 4-AP-naive subjects.

Conclusions. The administration of a single dose of an immediate-release formulation of 4-AP to humans with longstanding, traumatic quadriplegia is associated with sustained, clinically meaningful, and statistically significant improvements in pulmonary function. We suggest that the administration of 4-AP may have a salutary effect in patients suffering from SCI and appears to be associated with potentially clinically significant reductions in the pathophysiologic pulmonary sequelae of SCI.

(Pharmacotherapy 1997;17(3):415–423)

From the Medicine Service (Dr. Segal) and Research Service (Ms. Brunnemann), Department of Veterans Affairs Medical Center, Long Beach, California; and the College of Medicine, University of California, Irvine, California (Dr. Segal).

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Presented as an abstract at the 42nd annual conference of the American Paraplegia Society, September 3–5, 1996, Las Vegas, Nevada.

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Impaired pulmonary function is a pathophysiologic sequela of cervical spinal cord injury (SCI). Spirometry and static lung volumes and capacities are altered at the time of injury.[1] Diminished respiratory muscle strength causes decreases in maximal expiratory pressure (MEP) and maximal inspiratory pressure (MIP) and contributes to the morbidity and mortality of both the acute and chronic phase of injury.[1–3] A restrictive defect in pulmonary function caused by paralysis of the muscles of respiration predominates during the period of spinal shock and persists throughout the lifetime of the

Table 1. Patient Characteristics

Gender	Injury Level[a]	Injury Duration (yrs)	Age (yrs)	Height (cm)	Weight (kg)
M	C_{4-5} incomplete	8	46	172.7	69.6
M	C_5 incomplete	26	45	190.5	100.0
M	C_2 incomplete	9	38	175.3	69.1
F	C_{5-6} incomplete	13	29	157.5	47.7
M	C_7 incomplete	28	60	181.6	65.9
M	C_{5-6} incomplete	5	33	180.3	81.8
M	C_{4-5} incomplete	8	28	177.8	70.5
M	C_{6-7} incomplete	10	57	180.3	78.6
F	C_{4-5} complete	14	34	163.8	54.6
M	C_{5-6} complete	26	44	175.3	90.9
M	C_{5-6} complete	3	26	185.4	84.1
Mean ± SD		14 ± 9	40 ± 12	176.4 ± 9.3	73.9 ± 15.3
M	T_{12}–L_1 incomplete	39	61	182.9	104.6
M	L_{2-4} incomplete	4	53	172.7	80.9
F	T_{3-5} incomplete	14	41	160.0	52.3
M	T_8 incomplete	9	59	182.9	90.0
M	T_{8-9} incomplete	8	36	170.2	79.6
M	T_{3-4} complete	6	42	170.2	55.9
Mean ± SD		13 ± 13	49 ± 10	173.1 ± 8.7	77.2 ± 20.0

[a]American Spinal Injury Association/International Medical Society of Paraplegia criteria.[16]

survivor of a cervical SCI. Recently, obstructive pulmonary disease of potential clinical significance associated with hyperreactive small airways has been described in cervical SCI.[4, 5] When respiratory failure supervenes, acute and chronic dependence on mechanical ventilatory assistance or phrenic pacing can become, arguably, the most debilitating and resource-consuming therapeutic interventions.[6] The restrictive component of pulmonary disease caused by a paralyzed diaphragm or respiratory muscle weakness impairs the clearance of bronchial secretions and predisposes victims of SCI to recurrent bronchopulmonary infections, life-threatening sepsis, and respiratory failure.[7]

Following SCI, many of the nerve axons that traverse the anatomical site of injury are preserved, but become demyelinated and nonfunctional.[8] Thus, a clinically significant, potentially reversible conduction block causing paralysis of the muscles of respiration can occur as a result of injury.

4-Aminopyridine (4-AP) is a potassium channel blocker capable of enhancing the propagation of action potentials in demyelinated neurons. It has been shown to facilitate the conduction of impulses within the damaged spinal cord of humans and animals.[9–13] This capability has been associated with modest improvements in electrophysiologic variables and clinically evident improvement in neurologic and sensorimotor function.[9, 11, 14] Because of the unique, potentially beneficial pharmacologic properties exhibited by 4-AP,[15] we initiated this study to test the hypothesis that 4-AP might cause similar, salutary effects demonstrable as an improvement in pulmonary function in humans with chronic SCI.

Patient Selection and Methods

Fourteen healthy men and three healthy women suffering from traumatic SCI for more than 1 year's duration (chronic SCI) volunteered for this study and were consecutively enrolled. They consisted of 11 quadriplegic patients (age and injury duration, 40 ± 12 years, and 14 ± 9 years, respectively) and 6 paraplegic patients (age and injury duration, 49 ± 10 years, and 13 ± 13 years, respectively) (Table 1). One paraplegic and three quadriplegic patients were neurologically complete (American Spinal Injury Association/International Medical Society of Paraplegia criteria).[16] Absolute contraindications to participation in this study included a history of seizures or epilepsy, or of an abnormal electroencephalogram; recreational drug use, including ethanol; treatment with bronchodilators, or anticholinergic (atropinic) or antihistaminic drugs; or pregnancy, or inadequate or unverifiable contraceptive measures. Patients resumed their usual sleep-wake cycle, level of function, eating

patterns, and daily activities not sooner than 3 hours after ingesting a single dose of the study drug. All studies were initiated following an overnight fast and at the same time of day to minimize the influence of diet and circadian variability, respectively. Institutional review board approval and the written informed consent of each participant were obtained.

After pretreatment pulmonary function tests were performed, each subject ingested 10 mg of crystalline 4-AP (lot #P96-230-3; Regis Chemical Company, Morton Grove, IL) encapsulated with lactose in an immediate-release formulation. Pretreatment and follow-up pulmonary function tests were consecutively acquired and standardized spirometric measurements (Vitalograph Spirometer Model S; Vitalograph Medical Instrumentation, Lenexa, KS); MEPs and MIPs were serially measured according to the method of Black and Hyatt.[3] Measurements of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1:FVC ratio, MEP, and MIP were obtained in triplicate and followed for 24 hours using a sampling-rich strategy.

Statistical Analyses

The normality of the underlying distributions was tested using D'Agostino's robust D test, and tests of the significance of the differences between the means of continuous variables were carried out using repeated measures (randomized block) analysis of variance (ANOVA) or an appropriate nonparametric analysis based on the χ^2 test. The strength of association between injury level and pulmonary function tests was assessed using two-variable linear regression analysis. A probability (p value) below 0.05 was required to assign statistical significance to the

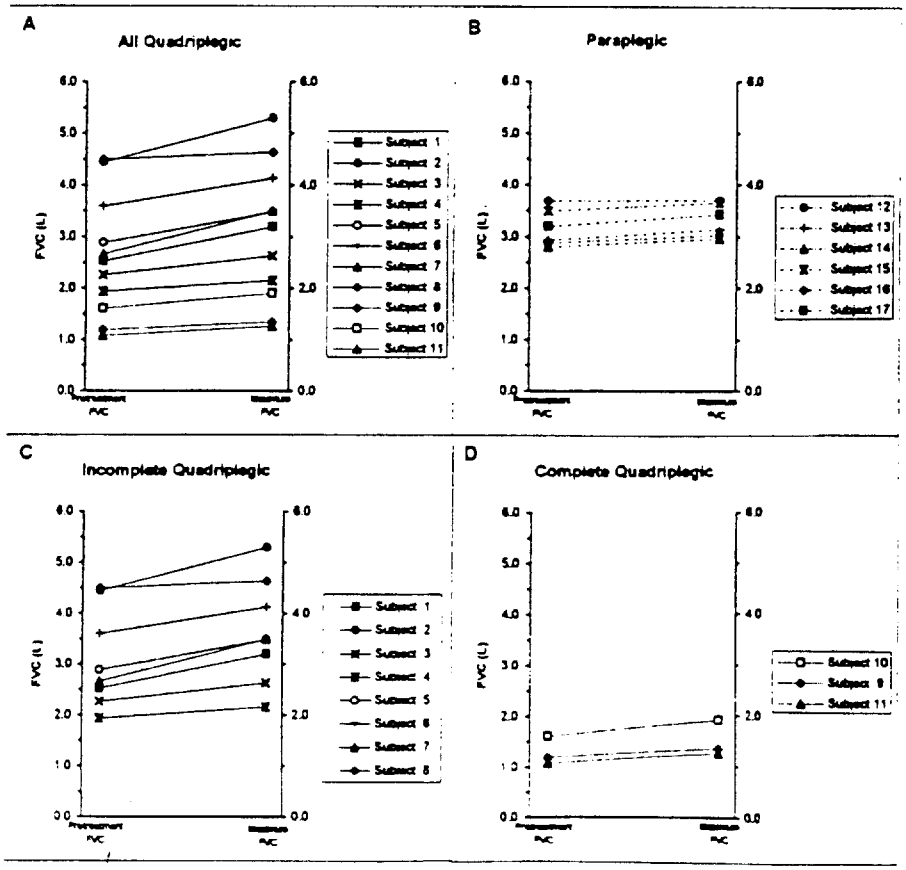

Figure 1. Maximum increases in FVC following the administration of a single, 10-mg dose of an immediate-release formulation of 4-AP. Patients with quadriplegia (Panel A) are easily distinguished from paraplegic patients (Panel B) by the magnitude of the increase in FVC. Panel C (quadriplegic, incomplete injury) and Panel D (quadriplegic, complete injury) are derived from Panel A. They provide a contrast and depict more clearly the magnitude of the increase in FVC between subgroups of patients with cervical SCI. Pretreatment values of FVC and the magnitude of the percentage change in FVC measured in patients with cervical cord injury may be useful in distinguishing between patients with complete or incomplete injury.

Table 2. Spirometry, MEP, and MIP: A Comparison of Predicted, Pretreatment, and Maximum Values in 17 Patients with Chronic SCI

Injury Level/Gender	Predicted FEV_1[a] (L)	Pretreatment FEV_1 (L)	Maximum[c] FEV_1 (L)	Predicted FVC[b] (L)	Pretreatment FVC (L)	Maximum[c] FVC (L)	Pretreatment MEP (cm H_2O)
C_{4-5} incomplete/M	3.65	2.06	2.85	4.56	2.53	3.20	48.00
C_5 incomplete/M	4.48	2.79	3.95	5.59	4.45	5.30	40.67
C_2 incomplete/M	3.99	1.45	2.05	4.91	2.27	2.63	21.00
C_{5-6} incomplete/F	2.86	1.82	2.08	3.41	1.94	2.16	36.33
C_7 incomplete/M	3.55	2.98	3.16	4.55	2.89	3.49	89.00
C_{5-6} incomplete/M	4.36	2.99	3.22	5.32	3.60	4.13	22.67
C_{4-5} incomplete/M	4.36	2.8	3.36	5.27	2.67	3.50	46.67
C_{6-7} incomplete/M	3.61	3.74	3.86	4.60	4.50	4.64	104.50
C_{4-5} complete/F	2.99	0.78	0.99	3.60	1.19	1.35	20.33
C_{5-6} complete/M	3.82	1.19	1.46	4.76	1.61	1.91	43.67
C_{5-6} complete/M	4.79	1.36	1.51	5.77	1.08	1.26	108.00
T_{12}–L_1 incomplete/M	3.56	2.29	2.42	4.57	2.88	3.03	55.33
L_{2-4} incomplete/M	3.44	2.73	2.77	4.35	2.94	3.14	76.00
T_{3-5} incomplete/F	2.69	2.27	2.51	3.30	2.80	2.96	60.33
T_8 incomplete/M	3.64	3.02	3.03	4.65	3.50	3.66	90.33
T_{8-9} incomplete/M	3.81	3.07	3.44	4.68	3.69	3.70	75.00
T_{3-4} complete/M	3.66	2.57	2.69	4.54	3.20	3.43	88.00

[a]Males: $FEV_1 = Ht^2(1.541 - 4.06 \times 10^{-3}\ age - 6.14 \times 10^{-5}\ age^2)$; females: $FEV_1 = Ht^2(1.322 - 4.06 \times 10^{-3}\ age - 6.14 \times 10^{-5}\ age^2)$. American Thoracic Society.[17]

[b]Males: $FVC = Ht^2(1.75 - 1.35 \times 10^{-4}\ age - 1.01 \times 10^{-4}\ age^2)$; females: $FVC = Ht^2(1.463 - 1.35 \times 10^{-4}\ age - 1.01 \times 10^{-4}\ age^2)$. American Thoracic Society.[17]

[c]$p \leq 0.05$, pretreatment vs maximum.

difference between means or medians. Mean data are expressed as the mean ± 1 standard deviation unless otherwise indicated. Clinically meaningful changes in pulmonary function tests, as distinguished from numerical or statistically significant increases, were defined using the conventions adopted by the American Thoracic Society (ATS).[17] Standard nonlinear equations were used to predict FEV_1 and FVC as a function of chronologic age, height, and gender.[17]

Results

Statistically significant increases in mean FEV_1 and FVC were demonstrated in all 11 quadriplegic patients beginning 6 hours after the administration of a single 10-mg dose of an immediate-release formulation of 4-AP. Each of the statistically significant increases in spirometry also met the published ATS percentage criteria for defining clinical utility or a clinically meaningful pharmacologic response (Table 2). Increases in FEV_1 and FVC (Figure 1) meeting ATS criteria persisted for 12 hours after dose administration. The FEV_1:FVC ratio did not change appreciably from pretreatment in patients with quadriplegia. In contrast to pretreatment values, mean MEP and MIP reached a maximum at 10 and 8 hours, respectively, following 4-AP administration. These increases in respiratory pressures were statistically significant. Mean MEP went from a 10% increase at 4 hours into the study to a maximum of 22% ($p=0.03$) in all quadriplegic patients; it then declined to 14% at 12 hours and continued to demonstrate an 11% increase over pretreatment levels at 24 hours (Figure 2). Mean MIP in all quadriplegic patients went from a 13% increase in negative pressure at 6 hours to a maximum increase of 20% ($p=0.06$) at 8 hours and remained elevated to 13% over the pretreatment value at 12 hours into the study. Spirometry, MEP, and MIP in the eight quadriplegic patients with incomplete injury demonstrated a similar time course, but were larger numerically prior to treatment with 4-AP and at each time of measurement thereafter (Figure 2).

Statistically significant associations between changes in spirometry, MEP, MIP, and the independent variable injury level were demonstrated in patients with SCI prior to and following 4-AP administration. Significant associations with correlation coefficients (r values) greater than 0.82 ($p<0.02$) were demonstrated following treatment with 4-AP when percentage increase in MEP and change in FEV_1 as a percentage of FEV_1 predicted were regressed against the cord level of injury in quadriplegic patients with incomplete injury (Figure 3). In this same group of patients, r

Table 2. (continued)

Maximum[c] MEP (cm H_2O)	Pretreatment MIP (-cm H_2O)	Maximum[c] MIP (-cm H_2O)
98.00	65.67	65.00
99.00	52.33	107.00
56.33	31.33	63.67
45.00	66.17	68.67
81.00	61.40	74.00
41.33	60.67	98.00
83.67	65.33	83.67
107.00	86.00	106.67
25.00	49.67	55.00
68.00	62.33	92.50
101.33	62.00	56.67
79.00	35.67	54.67
73.33	42.67	69.33
70.33	63.00	80.67
119.67	78.83	101.50
98.00	52.67	65.67
105.00	61.33	64.33

values greater than 0.72 were calculated for the association between injury level and FEV_1 or the percentage change in measured FEV_1. Among all quadriplegic patients, significant associations with r values greater than or equal to 0.71 were observed between percentage increase in MEP or percentage increase in FEV_1 and the level of the cervical cord injury. The linear regression equation relating time elapsed from pretreatment measurement of FEV_1 to the highest value attained yielded a correlation coefficient of 0.78 ($p<0.001$) in all 17 subjects with SCI (Figure 3).

No statistically significant changes over pretreatment spirometry, MEP, or MIP were observed among paraplegic patients followed for 24 hours after ingesting 4-AP. Moreover, pretreatment pulmonary function testing could not distinguish paraplegic from quadriplegic subjects, statistically, although numerical differences suggestive of trends were noted (Table 2). Pretreatment spirometry (FVC, FEV_1) in paraplegic or quadriplegic subjects was significantly lower than values predicted from standard equations derived in healthy, able-bodied (intact neuraxis) volunteers. The paraplegic patients, nevertheless, could be used as an internal control population in whom the consistent lack of response and an overall flat response curve to 4-AP support the absence of any change in pulmonary function attributable to a "learning effect." All patients with cervical SCI (quadriplegia) were readily distinguishable from patients with thoracolumbar injury (paraplegia) when time (hours) to attain maximum values of FEV_1, FVC, MEP, and MIP was compared between groups ($p<0.05$). In contrast to quadriplegic patients, significant linear correlations between injury level and MEP, MIP, or spirometry were not observed in patients with paraplegia.

Discussion

The results of this study clearly support the conclusion that 4-AP appears to improve pulmonary function in patients with quadriplegia. Subsequent to the administration of 4-AP,

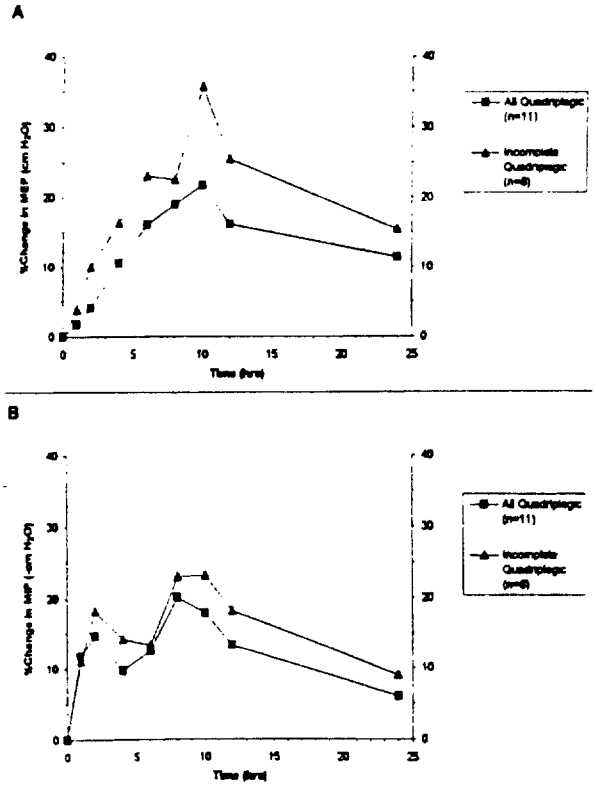

Figure 2. (Panel A) The time-course profiles of the mean percentage change in maximal expiratory pressure (MEP) following the administration of 4-AP to all quadriplegic patients (■) or quadriplegic patients with incomplete injury (▲) are superimposed on the same axes. Patients with incomplete injury demonstrated a greater response to 4-AP at each time point. Differences between curve maxima at 10 hours were statistically significant as were the differences between the maximum value and pretreatment value of MEP. (Panel B) Mean percentage change with time in maximal inspiratory pressure (MIP) compared with the pretreatment value is contrasted between all quadriplegic patients (■) and incomplete (▲) cervical cord injury. Maximum increases in negative pressure and the magnitude of the changes in MIP, in general, were less than those observed in MEP. A statistically significant ($p\leq 0.05$) difference between MIP pretreatment and at the time when the maximum change in MIP occurred (8 hrs) was demonstrated in patients with incomplete quadriplegia

statistically significant, clinically meaningful responses[17] occurred in patients with longstanding cervical SCI. For the first time, to our knowledge, a mechanism-based pharmacologic intervention has demonstrated efficacy in enhancing respiratory muscle function and improving ventilatory mechanics in spinal man.

Spinal cord injury is a devastating clinical condition that profoundly affects numerous organ systems and results in a lifelong impairment of homeostasis.[18–20] Traditionally, many of the pharmacologic interventions used in treating the medical and physiologic consequences of SCI have been directed toward diminishing spasticity and pain, or treating sepsis and the complications of prolonged immobility (e.g., pressure ulcers).[21] The mechanisms mediating these pathophysiologic sequelae of SCI are often unknown or not directly amenable to treatment, and drug therapy often is directed only toward modifying the disabling or debilitating consequences of injury in a relatively nonspecific fashion. Hence, disabling, high-profile, easily demonstrated and measured comorbidities or complications such as impaired voluntary motor function (paresis), pain, and spasticity have been accorded priority status in the hierarchy of postinjury residuals to be targeted for therapeutic intervention. However, the consequences of a demodulated or failed autonomic nervous system subsequent to SCI[18, 20–24] may underlie or mediate any or all of these impairments and comorbidities.

The myriad manifestations of autonomic failure are often not well recognized or adequately addressed. Many are often subclinical

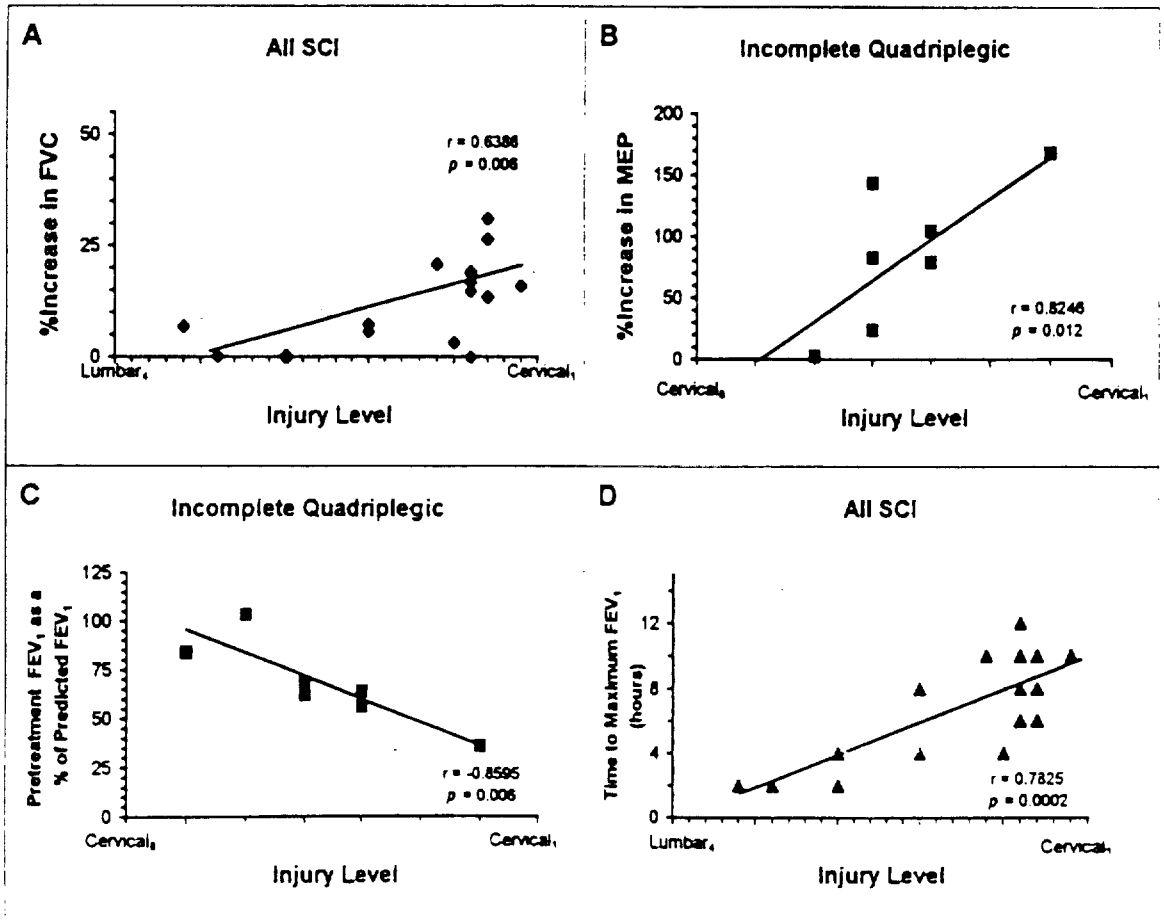

Figure 2. Strong, statistically significant associations between injury level and FVC, FEV_1, or MEP are depicted. Associations with injury level were demonstrated among all patients with SCI studied (Panel A and D) and in incomplete cervical cord injury (Panels B and C). When validated, the equations relating injury level and changes in spirometry or MEP will assist in predicting individual spirometric results when an injury level is known or vice versa, stratify patients by injury level using the results of one or more easily acquired measurements of pulmonary function. Physiologically based characterization and classification of injury level is dynamic, quantitative, and less subjective than the traditional bedside neurological examination.

and frequently devoid of easily demonstrable or well-recognized physical signs or symptoms, overt pathophysiologic changes, or socioeconomic consequences. They are thus less visible to clinicians and patients alike. Although the pathophysiologic sequelae of autonomic failure are reflected in altered cardiopulmonary function,[25] hemodynamic instability (autonomic dysreflexia),[23] dysregulation of involuntary motor function (e.g., altered gastrointestinal motility[22]), impaired respiratory function,[2, 4, 5] and cardiac dysrhythmia,[26] being "less evident" clinically, these changes in physiology often go unrecognized or are treated as though of negligible importance. They are, arguably, of no less significance, and in most instances are more likely to contribute to disrupting homeostasis and increasing morbidity and mortality than the clinically more evident consequences of SCI such as pain, spasticity, and impaired mobility.

Measurements of FEV_1, FVC, FEV_1:FVC, MIP, and MEP can be used to identify and distinguish respiratory muscle paralysis from obstructive components of pulmonary disease.[3] Changes in spirometry and respiratory muscle function previously have been demonstrated in patients with SCI as have correlations between spirometry or static lung volumes and injury level.[1, 4, 5, 27] The results of this study confirm these findings and support the conclusion that 4-AP is an effective drug treatment that improves pulmonary function subsequent to SCI.

We believe that our findings of increases in spirometry and enhanced respiratory muscle function in patients with quadriplegia are attributable to the pharmacologic actions of 4-AP. The results of this study are consistent with our understanding of the putative mode of action of 4-AP in facilitating central nervous system conduction in preserved, demyelinated axons and in enhancing synaptic transmission. The increases demonstrated in FEV_1 and FVC following 4-AP administration were significant both in terms of statistical and ATS criteria.[17] The persistence of these changes in spirometry for up to 12 hours after a single 10-mg dose was unanticipated and has not previously been demonstrated. And although 4-AP has been shown to reduce spasticity in skeletal muscle, direct effects on bronchial smooth muscle or small airway reactivity to challenge has not been reported.[14, 15]

Recent studies of the pharmacokinetic behavior of 4-AP in spinal man have demonstrated evidence of enterosystemic recirculation, delayed systemic excretion, and an increase in the terminal elimination half-life of 4-AP consistent with our observation of an extended pharmacologic effect.[14] These SCI population-specific changes in 4-AP drug disposition kinetics could also provide an explanation for the increase in time to onset of peak drug activity and the prolonged effect observed.

The strongest associations between neurologic level of injury and measures of pulmonary function were observed in quadriplegic patients with incomplete injury (Figure 3). Furthermore, the greatest percentage increase or return toward normal respiratory function was seen in incomplete quadriplegic patients who had the highest neurologic level of injury. We interpret this observation to suggest that the amount of potentially restorable pulmonary and/or neurologic function is not necessarily dictated by the clinically assessed injury level or the degree of paralysis. In individual quadriplegic patients, most notably those with complete injury or very low pretreatment values for spirometry, increases in response to 4-AP never reached predicted values. The correlation between injury level and FEV_1 in quadriplegic patients naive to 4-AP was derived from a simple linear equation that allows injury level to be predicted from pretreatment FEV_1, or FEV_1 to be predicted from injury level. Using these predictive relationships and easily obtainable measurements of pulmonary function, a physiologically based and quantitative estimate of the level of injury can be derived. For example, knowing that the magnitude of FEV_1 in untreated patients with SCI varies monotonically with injury level ($r=0.73$) will have applicability in predicting the level and completeness of injury in individual patients. Simple mathematical relationships between injury level and serial measurements of percentage or absolute changes in spirometry, MEP, or MIP following therapy with 4-AP were identified in this study. These relationships can help to identify patients with SCI who are likely to demonstrate the greatest clinical response to 4-AP, the level and completeness of their injury, and the degree of response to be anticipated at a given plasma 4-AP concentration.

Our results demonstrate that with reasonable certainty, an accurately characterized injury level in a quadriplegic patient suffering from an incomplete injury can be used to predict the magnitude of the change in pulmonary function to be expected from a single 10-mg dose of 4-AP

(Figure 3). Ultimately, all of this information can be incorporated into SCI population-specific models that will have diagnostic or prognostic value, serve to guide therapies, and have usefulness in directing our inquiries into injury level-dependent mechanisms. Currently, assessing the completeness of injury in patients with SCI, with particular reference to the identification of preserved neurons and their potential for responding to 4-AP, is dependent on a technique that employs lowering core body temperature to elicit changes in the patterns and magnitude of evoked potentials.[28] Response to a single dose of 4-AP may offer a useful alternative method of investigation and classification.

Changes in the FEV_1:FVC ratio following treatment were not observed suggesting that a proportional increase in both measurements had occurred (Table 2). The changes in spirometry demonstrated after the administration of 4-AP to patients with quadriplegia were not seen in paraplegic volunteers. Our inability to demonstrate significant changes in pulmonary function in paraplegic patients following the administration of 4-AP is best attributed to lack of sensitivity in our battery of tests and intersubject variability that we believe is greater and more confounding in individuals with paraplegia than in those with cervical cord injury. While mean values for FEV_1, FVC, MIP, and MEP were numerically lower in quadriplegic patients than in paraplegic patients, and much lower in SCI subgroups than values calculated from predictive equations derived in able-bodied populations, no statistically significant or clinically meaningful differences between SCI subgroups were demonstrated (Table 2).

Among paraplegic patients, in contrast to quadriplegic patients, greater heterogeneity in terms of injury level, physiology, and completeness of injury prevented more than a strong trend ($p=0.06$) toward a significant difference in pretreatment spirometry from being demonstrated. Similar trends have been described by other authors and appear to distinguish paraplegic patients, even those with injury level below T_{12}, from the able bodied.[1, 27] Impaired pulmonary function and altered ventilatory mechanics have been observed in low paraplegia even when the injury was well below the efferent outflow to muscles of respiration. These changes have been attributed to deafferentation and loss of proprioceptive input from anatomically distant structures or organs below the injury level that generate sensory cues integral to maintaining respiratory function and cardiopulmonary homeostasis.[29]

Statistically significant increases in MIP and MEP were demonstrated in patients with quadriplegia following 4-AP administration (Table 2, Figure 2). Maximal expiratory pressure and MIP increased in all quadriplegic patients irrespective of the completeness of the injury, and a strong positive correlation between percentage increase in MEP and injury level was seen (Figure 3). Analogous to the changes we observed in spirometry, the largest increase in MEP or MIP occurred in patients with incomplete injury. Maximum increases in MEP of 36% and 22% were demonstrated 10 hours after the administration of 4-AP in incomplete and complete injury, respectively. A similar pattern was observed in the time course of the change in MIP during the 24-hour study interval (Figure 2). Changes in MIP and MEP correlate highly with changes in the mechanical force exerted by the muscles of respiration and are used as measures of respiratory muscle strength. As such, MIP and MEP are most reflective of the restrictive pulmonary disease caused by respiratory muscle paralysis subsequent to SCI.[3] Because 65% of the inspiratory increase in lung volume in the able bodied and as much as 90% of tidal volume in quadriplegic patients are dependent on the strength of contraction of the diaphragm,[30] it is reasonable to infer that the magnitude of the changes in MEP and MIP attributable to 4-AP are highly important and of potential clinical significance. Whether 4-AP increases respiratory muscle strength and endurance centrally through an effect on central nervous system respiratory centers and/or axonal conduction, or peripherally, by directly enhancing involuntary smooth muscle function or neuroneuronal and neuromuscular transmission, remains to be ascertained.

The clinical implications of the results of this study are diverse, significant, and consonant with a therapeutic role for 4-AP in patients with SCI. The administration of single dose of an immediate-release formulation to humans with longstanding, traumatic quadriplegia was associated with a sustained, clinically meaningful treatment effect and a statistically significant improvement in respiratory function.

We suggest that the administration of 4-AP should have a salutary effect in these patients and that its value as a pharmacologic intervention will be demonstrated through clinically significant reductions in the pathophysiologic pulmonary sequelae of SCI.

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Orally Administered 4-Aminopyridine Improves Clinical Signs in Multiple Sclerosis

Floyd A. Davis, MD, Dusan Stefoski, MD, and Jean Rush, RN, MSN

4-Aminopyridine (4-AP), a potassium channel blocker, restores conduction in blocked, demyelinated animal nerve. Its administration to multiple sclerosis (MS) patients produces transient neurological improvements. Vision improves after either oral or intravenous administration, whereas motor function improvement has been reported only with the latter. To assess further its potential as a practical symptomatic treatment, we studied the efficacy of single, oral doses of 4-AP on both visual and motor signs in MS. Twenty temperature-sensitive male MS patients were given either 10 to 25 mg of 4-AP or identically appearing lactose placebo capsules. Static quantitative perimetry, critical flicker-fusion, visual acuity, visual evoked potentials, and videotaped neurological examinations were monitored. All of 15 MS patients given 4-AP mildly to markedly improved. Motor functions (power, coordination, gait) improved in 9 of 13 involved, vision in 11 of 13, and oculomotor functions in 1 of 2. Improvements developed gradually at doses as low as 10 mg, usually beginning within 60 minutes after drug administration, and reversed gradually over 4 to 7 hours. No serious adverse effects occurred. No significant changes were observed in 5 MS patients given placebo. We conclude that orally administered 4-AP produces clinically important improvements in multiple, chronic deficits in MS. Further studies are warranted to assess efficacy and safety of prolonged administration.

Davis FA, Stefoski D, Rush J. Orally administered 4-Aminopyridine improves clinical signs in multiple sclerosis. Ann Neurol 1990;27:186–192

Computer simulation studies indicate that conduction block in demyelinated axons is due to a critical decrease in action current that results from its wasteful short-circuiting through bare axonal internodes [1]. A strategy for developing a symptomatic therapy in multiple sclerosis (MS) would be to attempt to restore conduction in blocked demyelinated axons by increasing action current [2–5]. Drugs that increase action potential duration either by inhibiting sodium channel inactivation or potassium channel activation, or both, increase action current and would be expected to restore conduction in blocked demyelinated nerve [6]. 4-Aminopyridine (4-AP), a blocker of K^+ channel activation [7], prolongs nerve action potentials and, as predicted, restores conduction in blocked demyelinated nerves in animals [8–11]. Orally administered 4-AP has also been shown to improve vision but not motor function in MS patients by Jones and associates [12], and we subsequently reported that intravenous 4-AP improves motor and oculomotor as well as visual deficits in MS [13]. The purpose of this study is to assess further the efficacy and safety of oral single-dose 4-AP and also to determine if prolonged therapeutic trials are warranted.

As in the previous investigations with 4-AP, temperature-sensitive patients [14, 15] were selected because they are also expected to be very sensitive to pharmacological conduction modifiers [6, 13]. The number of MS patients who are temperature sensitive is substantial. Malhorta and Goren [16] observed worsening during induced hyperthermia (hot-bath test) in 17 of 20 MS patients (85%). Simons [17] reported that 62% of patients with MS became weak when they were exposed to heat.

Methods

Protocol and Patient Assessment

Twenty temperature-sensitive male MS patients were evaluated before and after oral administration of either 4-AP (2.5- and 5-mg capsules) or identically appearing lactose placebo. Their ages ranged from 25 to 48 years (median, 36.5). 4-AP was purchased from Regis Chemical Company (Morton Grove, IL), and 4-AP and placebo were formulated into capsules by our hospital pharmacy. The 10- to 25-mg dose range was systematically explored according to a descending-ascending schedule, with individual total doses of 25, 20, 15, 12.5, and 10 mg (Table 1). The dose range was based in part on our previous experiences with intravenous administration of 4-AP [13]. 4-AP was administered orally as a single dose except in 3 patients, who received multiple doses over 60 to 90 minutes. Patients were not told whether they received 4-AP or placebo; 15 received 4-AP and 5 received placebo. They were informed of possible 4-AP side effects, including paresthesias, which commonly occur [12, 13], but the frequency of occurrence was not discussed. They were also told

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Table 1. Summary of Results of Oral 4-Aminopyridine and Placebo Administration to MS Patients

Patient	Agent	Total Dose (mg)	Motor Function	Vision	Oculomotor Function	VEP	Side Effects	Net Effect
1	4-AP	20	3+	1+			P,D	Y
2	4-AP	20	2+	2+			D	Y
3	4-AP	25	3+	2+			D	Y
4	4-AP	15	1+				P,D	Y
5	4-AP	15	2+				D	Y
6	4-AP	10	2+	2+			P,D	Y
7	Placebo		0				N	N
8	4-AP	10	3+	0			D	Y
9	4-AP	10		3+			N	Y
10	4-AP	10		3+		Y	D	Y
11	Placebo			0	0	N	N	N
12	4-AP	12.5	0	2+	0	N	N	Y
13	4-AP	15	1+	0		N	N	Y
14	4-AP	15	0	3+		Y	P,D	Y
15	4-AP	20	0	3+		Y	P,D	Y
16	4-AP	12.5	2+	1−		N	N	Y
17	4-AP	20	0	3+	2−	Y	N	Y
18	Placebo		0	0	0	N	N	N
19	Placebo		0	0		N	N	N
20	Placebo		0	0	0	N	N	N

AP = aminopyridine; VEP = visual evoked potential; 0 = no improvement; 1− = mild improvement; 2+ = moderate improvement; 3+ = marked improvement; P = paresthesias (transient, mild); D = dizziness and/or lightheadedness (transient, mild); Y = improvement; N = no ch[illegible] Blank spaces indicate that testing was not performed because of lack of sufficient testing time or that function was normal or not te[illegible]ture sensitive.

that placebo, although inactive, might be associated with similar side effects. Only one of the investigators (D.S.), whose role was largely supervisory during the testing, was aware of the nature of the agent administered and the dose schedule. The other investigators (F.A.D., who graded the videotaped neurological examinations [VNE], and J.R.) were blinded except during an initial pilot series of the first 4 patients, who were all given 4-AP (Table 1, Patients 1–4).

While overall neurological status was examined, testing focused on temperature-sensitive, functionally relevant deficits. Each patient's serially recorded videotapes were graded during a single session to facilitate comparisons and were rated on a scale of 0 to 6 (Table 2), reflecting the range between normal function (grade 0) and severe deficit (grade 6). Motor improvements of 2 grades were considered significant and were rated as 1+. Three grades and greater improvements were rated as 2+ and 3+, respectively.

Critical flicker-fusion frequency (CFF) was tested monocularly wi'h a Grass model HPS-2-B photo-stimulator (Quincy, MA) [13]. Visual acuity (VA) was assessed monocularly by determining the minimum resolvable separation of two vertical oscilloscope traces [13]. The results from six trials were averaged for CFF and for VA. Visual improvements, as measured by CFF and VA, were assessed as 1− when the postdose increase was 15 to 30% of the predose v[illegible] 2+ for a 31 to 45% increase, and 3+ for an increase greater than 45%.

Visual field examinations were carried out on a Goldmann perimeter 940-ST (Haag-Streit AG, Bern, Switzerland) using standard techniques for static quantitative perimetry. Visual evoked potentials (VEPs) were recorded with a Nicolet

Table 2. Videotape Ratings

Grade	Function
0	Normal
1	Between normal function and mild deficit, dysfunction is revealed only on very thorough testing; it is often fleeting and not noticeable to the patient
2	Mild deficit, detectable on routine testing of a specific function; it only minimally alters the patient's performance in carrying out a given task
3	Mild to moderate deficit, readily demonstrable on testing; it mildly but noticeably alters a specific function
4	Moderate deficit; the specific function can only be partly executed by the patient
5	Moderate to severe deficit; the patient can only minimally perform the given task at a functionally useful level
6	Severe deficit; the specific neurological function is nearly or completely abolished and serves no significant functional use

Pathfinder II averager (Madison, WI) using checkerboard pattern reversals from a Nicolet 1005 Visual Stimulator. Monocular full and central field stimulations were carried out with each pattern element subtending 22 minutes of arc and a reversal rate of 1.88 Hz. Potentials were recorded from O_z electrode with Fp_z as reference and C_z as ground. For each field, 400 stimuli (2 sets of 200) were averaged. Upper-limit-

normal P-100 latency values for our laboratory are 111.34 msec for full-field and 114.92 msec for central-field stimulation, each representing a mean plus 2 standard deviations. P-100 latencies were measured with a manually adjustable electronic cursor, and wave amplitudes were measured peak-to-peak between N-1 and P-100. Vital signs, including body temperature, electrocardiogram, electroencephalogram, complete blood count, and serum biochemistries (SMA-18), were monitored intermittently in all patients.

Patient Selection

Patients were selected from the Rush Multiple Sclerosis Center (Rush–Presbyterian–St. Luke's Medical Center) using the following criteria: a definite diagnosis of MS; male, not older than 47 years; no history of cardiac, pulmonary, hepatic, renal, or other systemic disease; and a positive history for the presence of neurological signs that reversibly worsen with hyperthermia. Only men were studied in compliance with Food and Drug Administration restrictions. This study was approved by our institution's Human Investigation Committee and all patients signed informed consent forms.

Results

Mild to marked improvements occurred in all of the 15 MS patients given 4-AP. Motor functions improved in 9 of 13 involved, vision in 11 of 13, and oculomotor function in 1 of 2. Improvements developed gradually with doses as low as 10 mg 4-AP, usually beginning within 60 minutes after drug administration, and reversed gradually over 4 to 7 hours. No significant changes or side effects occurred in the 5 patients who received placebo (see Table 1).

Motor functions improved most strikingly with respect to power and coordination. All limb muscle groups appeared susceptible. These improvements were apparent with both simple function tests and the performance of complex motor tasks such as gait and repetitive movements.

Figure 1 shows improvement in the ability to raise the arms against gravity after receiving 20 mg 4-AP in a 38-year-old MS patient (see Table 1, Patient 1) with a moderate-to-severe quadriparesis caused by spinal cord involvement. The peak effect lasted 1.5 hours and the patient temporarily regained the ability to feed himself. Reversal occurred about 6 hours after drug administration.

In asymmetrically affected limbs, improvements with 4-AP were often greater in the limb that was less severely involved (see Fig 1). Also, asymmetrical improvements were sometimes observed in similarly affected limbs. Improvements often resulted in significant functional gains. Patients usually noticed the improvements as they were occurring but sometimes only as they were wearing off. Less commonly, patients were either not sure of documented improvements or noted some but not others.

Visual improvements occurred in 11 of 13 patients who received 4-AP and in none of the placebo control

Fig 1. Videotape frames of arm-raising ability after 20 mg 4-AP administration in an MS patient with severe quadriparesis caused by spinal cord involvement. Before 4-AP (A), 2 hours after 4-AP (B), and 6 hours after 4-AP (C). Improvement is more pronounced in the less affected right upper extremity (B). Reversal occurs sooner in the more severely affected left arm (C).

subjects. Patients whose visual tests improved after 4-AP administration were also generally aware of an improvement in vision. Figure 2 illustrates improvement of left-eye CFF from 23 Hz to 40 Hz 1.5 hours after 10 mg 4-AP in a 42-year-old MS patient with optic neuropathy (see Table 1, Patient 10). Normal subjects fuse at about 40 Hz in our laboratory. Gradual reversal to baseline occurred by 7.5 hours after drug administration. Transient mild lightheadedness was reported.

Full-field (FF) and central-field (CF) VEP tests were recorded in 11 patients (7 4-AP and 4 placebo) before and after the dose. We compared tracings predose (time 0) and postdose at about 2 hours, when clinical changes were usually apparent (Table 3).

All patients had abnormal predose FF and CF VEPs. The latter were often more severely affected, and in 3 patients some latencies could not be determined because of waveform distortions (see Table 3). In 1 patient (Patient 10) data storage difficulty precluded post–4-AP amplitude measurements, but bilateral increases were apparent on direct observation for all 4 responses.

Latencies improved in the 4-AP–treated group. The mean postdose P-100 latency change for FF and CF VEPs combined was a 5.40-msec decrease in the 4-AP

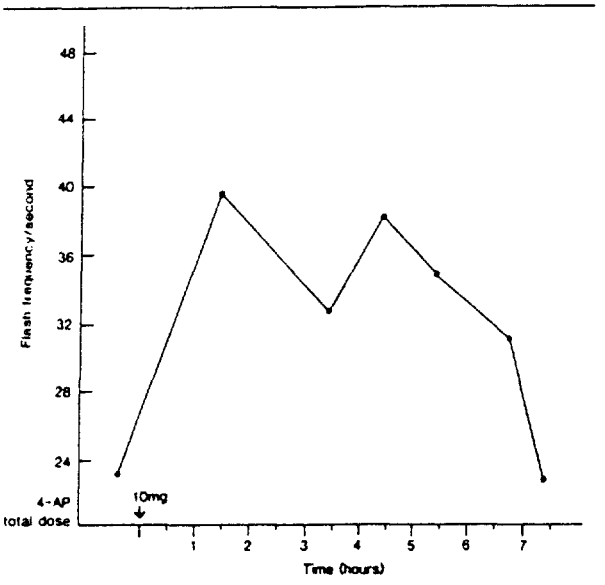

Fig 2. Improvement in critical flicker-fusion frequency after administration of 4-AP in an MS patient with left optic nerve involvement.

Table 3. Visual Evoked Potentials

			Full Field				Central Field			
			P-100 Latency (msec)		Amplitude (μV)		P-100 Latency (msec)		Amplitude (μV)	
Patient	Agent	Time (hr)	Left	Right	Left	Right	Left	Right	Left	Right
10	4-AP	0[a]	126.5	126.0	1.72	1.17	133.4	151.4	1.63	1.26
		2.3[b]	126.0	126.0	NA	NA	122.5	145.0	NA	NA
11	Placebo	0[a]	153.5	172.5	1.88	1.46	153.5	CND	1.04	CND
		2.4[b]	154.5	172.5	1.45	1.14	156.0	CND	1.06	CND
12	4-AP	0[a]	142.5	174.5	1.34	3.11	168.5	182.0	2.51	0.90
		2.2[b]	141.5	177.5	1.64	2.26	168.5	CND	1.56	CND
13	4-AP	0[a]	137.0	159.0	1.52	3.16	143.5	CND	1.68	CND
		2.1[b]	136.0	157.0	1.54	2.78	CND	CND	CND	CND
14	4-AP	0[a]	127.0	127.0	3.33	3.62	126.5	126.0	2.41	1.72
		2.0[b]	124.0	122.0	4.31	3.83	119.0	123.0	1.79	2.69
15	4-AP	0[a]	150.5	166.5	1.46	1.19	156.0	171.5	0.96	0.83
		2.0[b]	137.0	159.5	1.30	1.16	149.5	159.5	0.43	1.12
16	4-AP	0[a]	149.5	150.0	2.70	1.65	155.0	146.0	2.30	2.33
		2.5[b]	150.0	150.0	2.43	1.13	153.5	148.0	2.68	2.28
17	4-AP	0[a]	143.0	155.0	2.51	1.87	153.5	173.0	1.03	0.73
		2.3[b]	137.5	149.0	4.36	1.92	143.0	161.5	2.48	2.71
18	Placebo	0[a]	142.5	139.5	2.08	2.65	145.0	147.5	1.24	1.77
		2.0[b]	142.5	141.0	3.51	2.70	145.0	149.0	1.88	1.79
19	Placebo	0[a]	132.5	170.0	3.19	1.80	CND	CND	CND	CND
		1.8[b]	134.5	170.5	3.11	1.58	CND	CND	CND	CND
20	Placebo	0[a]	116.5	124.5	2.48	2.77	113.0	122.0	1.11	1.30
		1.9[b]	116.5	125.0	2.06	2.39	117.0	123.5	1.50	1.00

[a]Predose.
[b]Postdose.
NA = not available; CND = cannot determine.

group and a 1.12-msec increase in the placebo group ($p = 0.019$; 2 independent samples, t test). The post–4-AP CF P-100 latencies were decreased by a mean of 6.80 msec, whereas with placebo they were increased by a mean of 1.75 msec ($p = 0.012$). The FF P-100 latencies were decreased by a mean of 2.92 msec in the 4-AP group and increased by a mean of 0.69 msec in the placebo group ($p = 0.055$).

P-100 amplitude changes were much more variable from patient to patient than were the latencies and were not statistically significant. Mean increase for combined FF and CF amplitude was 0.43 μV in the 4-AP group and 0.34 μV in the placebo group ($p = 0.883$). The mean FF P-100 amplitude change was a 0.10-μV increase in the 4-AP group and a decrease of 0.09 μV in the placebo group ($p = 0.604$). The mean CF P-100 amplitude change was an increase in both the 4-AP and placebo group, by 0.48 μV and 0.18 μV, respectively ($p = 0.541$).

Employing the criteria of Hammond and Wilder [18] and Persson and Sachs [19], wherein latency changes of 5 msec or more and amplitude changes of 30% or more are considered to be significant, 4 of the 7 patients who received 4-AP had improvements. The P-100 latencies in these patients (see Table 3, Patients 10, 14, 15, 17) showed a decrease in 12 of 16 (75%) eye tests and an increased amplitude in 6 of 12 (50%) eye tests. These 4 patients also had simultaneous 3+ improvements of CFF and VA testing (see Table 1). The remaining 3 patients given 4-AP showed either insignificant improvements, no change, or worsenings of P-100 latencies and amplitudes. In comparison, none of the 4 placebo control subjects showed any significant P-100 latency improvements, while amplitude improvements occurred in 3 of 8 (38%) eye tests in 2 control subjects (see Table 3, Patients 18 and 20).

Four of 7 patients given 4-AP showed improvements in waveform configuration, such as clearer definition of N-1 and P-100 peaks, as depicted in Figure 3. This figure illustrates reversible improvements in VEP latency and waveform after a single dose of 20 mg 4-AP in a 41-year-old MS patient (see Table 1, Patient 17) with bilateral optic neuropathy. No side effects occurred. Values for P-100 latencies and simultaneously recorded CFF and VA for this patient are given in Table 4.

Clinical and electrophysiological improvements with 4-AP occurred predominantly in temperature-sensitive systems. In a few patients improvements occurred in systems for which there was no history to suggest temperature sensitivity: Patients 3 and 6 (vision) and Patient 10 (vision, VEP); see Table 1.

Ten of 15 patients who received 4-AP experienced transient mild paresthesias or dizziness-lightheadedness, or both (see Table 1). Paresthesias were mainly confined to the limbs but also occurred orolingually

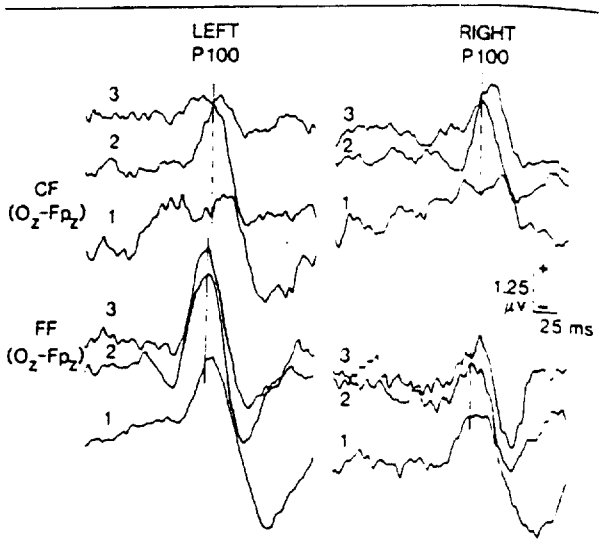

Fig 3. Reversible improvement in visual evoked potential (VEP) latency and waveform after a single dose of 20 mg 4-aminopyridine (AP) in a 41-year-old MS patient with bilateral optic nerve involvement. Vertical markers indicate the P-100 wave latencies for VEP-2 tracings. Latency improvements occur in all VEP-2 tracings. Waveform improvements (VEP-2) are particularly striking in the central field (CF) tracings, where the pre–4-AP VEPs (1) are barely discernible (VEP-1). There is also a marked reversible normalization of the N-1 wave (small, negative downward deflection preceding the major, positive P-100 upward wave) in the left full-field (FF) VEP-2 recording. Values for latencies and simultaneously recorded critical flicker-fusion and visual acuity improvements are given in Table 4. (2 = approximately 2.33 hours after 4-AP administration; 3 = approximately 4.33 hours after 4-AP.)

and in the scalp. Mild dizziness (not vertigo) or lightheadedness, or both, occurred at times with head-body movements. None of these symptoms were disturbing or interfered with the experimental procedure, and no patients requested to discontinue the study because of side effects. No significant side effects occurred in the 5 patients given placebo.

Discussion

The results demonstrate that orally administered 4-AP acutely improves both motor and visual abnormalities in MS patients. Some of the improvements were large enough to be of therapeutic benefit and occurred at well-tolerated doses. The possible use of oral 4-AP as a clinical treatment in MS requires further study to assess long-term efficacy, safety, and patient selection criteria.

While the clinical improvements with 4-AP are believed to be due to a restoration of conduction in blocked, demyelinated nerve fibers, it is possible that the ability of functioning demyelinated axons to conduct repetitive trains of impulses more faithfully is also improved. The CFF improvement with 4-AP in our

Table 4. Improvements Produced by a Single Dose of 20 mg 4-Aminopyridine in a 41-Year-Old MS Patient[a]

Test	Time (hr)	FF VEP P-100 Latency (msec)		CF VEP P-100 Latency (msec)		CFF (Hz)		VA Visual Angle (')[b]	
		Left	Right	Left	Right	Left	Right	Left	Right
1	0 (pre–4-AP)	143.0	155.0	153.5	173.0	18.3	15.0	4.3	3.5
2	2.33 (post–4-AP)	137.5	149.0	143.0	161.5	28.8	20.5	2.9	2.4
3	4.33 (post–4-AP)	137.5	158.5	151.0	172.0	27.1	18.5	3.3	2.8
4	5.50 (post–4-AP)	NT	NT	NT	NT	23.5	16.8	3.2	2.9

[a]Same patient and experiment as in Figure 3.
[b]Values are in minutes of arc.

FF = full field; VEP = visual evoked potential; CF = central field; CFF = critical flicker-fusion; VA = visual acuity; AP = aminopyridine; NT = not tested.

patients may reflect this. The repetitive conduction defect in demyelinated nerve [20–22] is the result of a decrease in membrane excitability caused by hyperpolarization produced by electrogenic Na^+ pumping [23], which 4-AP may counteract by increasing action current. Exactly where 4-AP exerts its effect on demyelinated axon has been widely theorized [13, 24, 25]. Based on K^+ channel localization [8, 26], it would be expected to be acting at or near demyelinated internodes.

It has been observed that repetitive impulse activity occurs in demyelinated axons exposed to 4-AP, which may account for 4-AP–induced paresthesias in humans [27, 28]. Ten of our 15 MS patients who received 4-AP experienced transient mild paresthesias or transient mild dizziness-lightheadedness, or both. Though these patients may have become unblinded, 3 had reversible improvements in VEP testing after 4-AP that cannot be explained by a placebo effect. This finding, the improvement in 4 of the patients given 4-AP who did not experience side effects, and the absence of improvements in the placebo group all strongly favor a true pharmacological effect. Finally, it is noteworthy that the videotaped neurological examinations, which were rated blindly, successfully differentiated the 4-AP and placebo groups.

The VEP improvements with 4-AP observed in this study are compatible with an improvement of conduction in demyelinated optic nerve fibers. VEP changes caused by putative alterations in optic nerve conduction have been demonstrated previously in MS patients. Improvement occurs with hyperventilation [29] and verapamil [30], while worsening occurs with increased body temperature [31] and exercise (Uhthoff symptom) [19]. Our findings with 4-AP are similar to the findings with hyperventilation reported by Davies and associates [29], who also observed P-100 latency reduction without consistent amplitude changes. The known greater variability of VEP amplitude compared to latency possibly explains this phenomenon [18, 32, 33].

Hammond and Yiannikas [34] reported markedly distorted and absent CF VEP responses in 34% of MS patients studied, which is consistent with preferential involvement of macular fibers in MS. This compares to similar findings in 27% of patients in our study. Improvements in CF waveforms seen with 4-AP are likely to reflect improvement in conduction in these macular fibers.

We have not observed serious or bothersome side effects at total intravenous doses of 4-AP below 30 to 35 mg [13] or single oral doses up to 25 mg reported here. In contrast, Jones and associates [12] stated that side effects (dysesthesias and dizziness) precluded its clinical use. While no seizures occurred among our patients or in the study by Jones and colleagues [12], seizures have been reported in patients who received 4-AP for treatment of myasthenia gravis [35], botulism [36], and MS [37]. Mechanisms for the convulsant action of 4-AP have been discussed previously [13]. Also, 3-aminopyridine is known to have convulsant action when applied directly on the cerebral cortex of cats [38]. Since MS patients have an increased incidence of seizures, they might be expected to be at higher risk for seizures on exposure to 4-AP than are normal subjects. Although it is important to recognize the potential for this side effect, our results suggest a safe and effective therapeutic window for orally administered 4-AP for visual and motor deficits in selected MS patients.

Patient selection criteria could be important with respect to 4-AP efficacy. Some patients might improve globally and others only in a specific neurological function, depending on the number and clinical expression of blocked demyelinated nerve fibers capable of being restored to conduction by pharmacological means. Temperature-sensitive MS patients are particularly favorable candidates for effective treatment with 4-AP because they have large numbers of nerve fibers that are either borderline-conducting or are just barely blocked [6]. Furthermore, during acute exacerbations in MS, temperature sensitivity is heightened [39].

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The effects of 4-aminopyridine in multiple sclerosis patients:

Results of a randomized, placebo-controlled, double-blind, concentration-controlled, crossover trial

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Article abstract—Because 4-aminopyridine (AP) improves residual deficits in some multiple sclerosis (MS) patients but has a narrow toxic-to-therapeutic margin, we compared the safety and efficacy of two target peak serum concentration ranges (low: 30 to 59 ng/ml and high: 60 to 100 ng/ml). We enrolled eight MS patients with temperature-sensitive visual and motor deficits in a randomized, placebo-controlled, double-blind, crossover trial of short-term oral AP treatment. We randomized patients to a sequence of three treatments on three separate days: placebo, low serum concentration, and high serum concentration. We determined dosing to achieve the desired steady-state peak serum concentration ranges from a test dose and population pharmacokinetic parameters using bayesian estimation. Contrast sensitivity, standard neurologic examination, ratings of videotaped neurologic examinations, and quantitative strength assessment all improved with treatment, but flicker fusion frequency, visual evoked response latencies, and Expanded Disability Status Scale scores did not. All patients experienced side effects during the high-serum-concentration arm. A grand mal seizure occurred at a serum AP level of 104 ng/ml, and an acute confusional episode occurred at 114 ng/ml. AP treatment produced improvements in residual deficits in MS patients, but the occurrence of significant toxicity suggests that AP serum levels should be monitored and peak levels above 100 ng/ml should be avoided. Concentration-control methodology may be useful in testing putative treatments for other neurologic diseases.

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Pathologic evidence of preserved axons in demyelinated multiple sclerosis (MS) lesions,[1] as well as reversibility of some MS deficits with temperature depression[2] and decreases in serum ionized calcium,[3] suggest that the neurologic dysfunction in MS is in part physiologic. Electrophysiologic studies of demyelinated axons showed that abnormal potassium currents decreased action potential duration and amplitude and contributed to conduction failure (reviewed in reference 4). Schauf and

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Bowris[5] first suggested that pharmacologic modification of sodium and potassium currents might be used to improve conduction in demyelinated fibers, and subsequent studies[4] showed that potassium channel blockers such as 4-aminopyridine (AP) improved nerve impulse conduction in experimentally demyelinated axons in vitro. Jones et al[6] reported the first study of AP in MS patients and showed that AP treatment caused improvement in temperature-sensitive visual deficits in five patients in an open-label trial. Stefoski et al[7] then showed that short-term intravenous AP treatment produced improvements in residual deficits in a larger number of temperature-sensitive MS patients in a placebo-controlled trial. Davis et al[8] demonstrated that short-term oral AP treatment was also effective, and Stefoski et al[9] showed that treatment duration of up to 5 days could be used without significant side effects. A randomized, placebo-controlled, double-blind, crossover trial in 68 patients[10] showed drug-related improvements in neurologic function without significant toxicity. However, two patients from that study who continued open-label AP had seizures, and one developed a treatment-related hepatitis (C. Polman, personal communication). Pharmacologic studies[11] showed clinical improvements in patients with peak levels in the 50 ng/ml range or higher, with some patients tolerating serum levels over 100 ng/ml. However, significant interpatient variability was noted (F. Davis, personal communication). This variability in pharmacokinetics coupled with the potential toxicity of AP could limit its widespread use in patients with MS.

Drugs such as AP, with large interpatient variability in pharmacokinetics and narrow toxic-to-therapeutic ranges, present a difficult dilemma in trial design. To avoid serious side effects in the patients having the highest serum drug levels, doses must be kept as low as possible, but this means that patients with the lowest drug levels may have levels inadequate to produce any therapeutic effect. An approach to this problem used in earlier trials of AP[7,8,10] is the escalating dose format. However, this may unblind patients and investigators if the drug has characteristic side effects, as is the case with AP. A new approach is concentration-controlled methodology, in which individual patients are administered the drug to achieve a predetermined target serum concentration range.[12] We used this methodology to test the efficacy and toxicity of two target serum concentration ranges of AP (30 to 59 ng/ml and 60 to 100 ng/ml) in eight MS patients with temperature-sensitive visual and motor deficits.

Methods. *Patient selection.* Eight patients with clinically laboratory-supported definite MS[13] who had objective deficits of visual acuity and lower extremity motor strength and tone were enrolled in the study. These deficits were, by history, both related to the patient's MS and worsened by temperature elevation but were stable for at least 30 days prior to randomization. Patients were excluded if they had a history of seizures or unexplained syncope, epileptiform activity on EEG, acute relapse within 3 months of randomization, corticosteroid treatment within 30 days of randomization, or complicating medical illness. Patients were required to abstain from corticosteroid and cytotoxic drugs during the study, and doses and schedules of other drugs were held constant during the trial. The study protocol was approved by the local institutional review board, and informed consent was obtained from all patients.

Measurement of serum AP levels. Serum samples were analyzed by a validated procedure based on a previously described method utilizing solid-phase extraction, high-performance liquid chromatographic separation, and ultraviolet detection.[14]

Treatment. Identical-appearing capsules were prepared (Elan Pharmaceutical Research Corp, Gainesville, GA) containing lactose or 2.5 or 5.0 mg of 4-AP (Regis Chemical Co, Morton Grove, IL) in lactose. Each patient received a 10-mg test dose of AP, and serum AP levels were serially monitored for 18 hours. The pharmacokinetic parameters for each patient were estimated using nonlinear regression techniques.[15] Patients were randomized 1 to 3 weeks later to a sequence of double-blind treatments: placebo, high concentration (60 to 100 ng/ml), or low concentration (30 to 59 ng/ml). The pharmacokinetic parameters obtained from the test dose were used, by an unblinded pharmacokineticist (D.Y., N.E., K.I.P.), to determine the initial dose for each treatment period for each patient. Timed serum AP concentrations were obtained after dosing during the blinded portions of the trial, and the pharmacokinetic parameters for each subject were reestimated using bayesian estimation techniques.[16] The bayesian a priori estimates for the calculation were obtained from a previous study (D. Young, personal communication). The pharmacokineticist was able to alter the dosage strength and interdose intervals as necessary to achieve the desired peak concentration at the time of evaluation (at 30 hours of treatment). Blinding was maintained by having the patient take active drug and placebo capsules at each dosing, by not announcing the dosing schedule to the caregivers in advance so that they would not be aware when changes in schedule were made, by making pseudoadjustments in the schedule during the placebo arm, and by having the unblinded pharmacokineticist and caregivers communicate by facsimile using forms prepared for the study.

Efficacy evaluation. Prospectively defined temperature-sensitive deficits of visual function and of lower extremity motor function were quantitated during each arm of the trial. Evaluations were carried out at the same time of day during each arm of the study, and body temperature was monitored.

The assessment of visual function included determinations of contrast sensitivity, flicker fusion frequency, and visual evoked response (VER) P100 latencies. Contrast sensitivity[17] was measured with a Pelli-Robson chart, with a different chart for each eye. Eyes with normal baseline values (>1.35) were not considered in the analysis. Psychological flicker fusion frequency was measured using a Grass stimulator and strobe light and expressed as the mean of quadruplicate determinations.[7] Eyes with normal baselines (>35 flashes per second) were not considered in the analysis. VER latencies were measured for each eye in triplicate on a Nicolet Pathfinder II with a 30-minute check size, a repetition rate of 1.5 per second, and 100 repetitions per determination. Tracings were read by a blinded reader and results expressed as the mean for each eye at each time point.

Table 1. Patient characteristics, AP dosage, and steady-state peak serum levels

Pt no.	Age	Sex	MS duration (yr)	EDSS	MS type	Study arm: Low concentration Dosage	Low concentration C_{max} (ng/ml)	High concentration Dosage	High concentration C_{max} (ng/ml)
1	51	F	20	3.0	CP	5 mg q12h	56	10 mg q6h	89
2	50	F	30	6.0	CP	7.5 mg q12h	35	12.5 mg q6h	104*
3	50	M	8	6.0	CP	7.5 mg q8h	64	12.5 mg q4h	114
4	62	M	12	6.5	CP	5 mg q6h	40	7.5 mg q4h	75
5	43	F	2	6.0	RP	5 mg q6h	37	7.5 mg q4h	68
6	35	F	8	8.0	CP	5 mg q12h	39	7.5 mg q4h	57
7	36	M	9	7.5	RP	7.5 mg q12h	47	10 mg q4h	87
8	41	M	17	5.0	CP	10 mg q6h	51	7.5 mg q6h	93
						Mean ± SE	46 ± 4		83 ± 6

EDSS Score on the Expanded Disability Status Scale.[20]
CP Chronic progressive.
RP Relapsing progressive.
* Dosing was terminated after 24 hours because of the occurrence of a seizure. This is the level at 24 hours and was not at steady state.

Eyes with baseline latencies in the normal range (<113 msec) were not considered in the analysis.

Lower extremity motor function was evaluated by physical examination and quantitative testing. The strength of the hamstrings and of the iliopsoas, quadriceps, gastrocnemius, and anterior tibialis muscles were evaluated by a blinded examiner and rated on the 0-to-5 Medical Research Council scale.[18] The "strength score" was the sum of the individual leg muscle ratings. A Kincom testing apparatus was used to further quantitate quadriceps and hamstring strength in isometric contraction.[19] Results were the mean of triplicate determinations of maximum force with a 60-second rest between determinations. At each time point, ambulation, as well as the examination of the lower extremities by the blinded examiner, were videotaped. Taped segments were later reviewed by two blinded raters (H.S.P. and S.D.-J.) who scored relative muscle strength, reflexes, and ambulation. The sum of the scores is given as the "videotape score."

The Expanded Disability Status Scale[20] (EDSS) score and ambulation index[21] (AI) were determined from the results of a standard neurologic examination and timed ambulation.

Data analysis. The Wilcoxon signed rank test was used to determine whether significant treatment-related improvements were seen.

Results. *Patient characteristics.* Eight MS patients (table 1) were treated in a concentration-controlled trial of short-term oral AP given in a randomized, placebo-controlled, double-blind format. The subjects consisted of four men and four women with ages ranging from 35 to 62 years, disease durations ranging from 2 to 30 years, and EDSS scores at entry ranging from 3 to 8. Six patients had a chronic progressive course, and two had a relapsing progressive course.

Effectiveness of concentration control. The ages and steady-state peak serum concentrations achieved during treatment are summarized in table 1. The mean C_{max} of 46.1 ng/ml for the low-serum-concentration arm and 83.3 ng/ml for the high-serum-concentration arm fell within the intended concentration ranges. The observed C_{max} was within the desired range in seven of eight patients for the low-concentration arm and five of eight patients for the high-concentration arm. A retrospective analysis of intrapatient variability suggests that food interfered with absorption and was responsible for much of the observed aberrant concentrations (data not given).

Toxicity. AP treatment was associated with serum concentration-related side effects. Overall, seven adverse events were recorded during the placebo arm, nine during the low-concentration arm, and 36 during the high-concentration arm. Dizziness was the most common toxic effect, occurring once in the placebo arm, three times in the low-concentration arm, and 11 times in the high-concentration arm. Paresthesias were not reported during the placebo arm, but occurred four times in the low-concentration arm and nine times in the high-concentration arm. Nausea was reported once during the placebo arm, once during the low-concentration arm, and five times during the high-concentration arm. Nervousness or anxiety was reported only during the high-concentration arm. Two serious adverse events occurred, both during the high-concentration arm. An episode of encephalopathy occurred in patient 3 when serum AP peaked at 114 ng/ml. A grand mal tonic-clonic seizure occurred in patient 2 when serum AP peaked at 104 ng/ml. Not only were side effects more common in the high-serum-concentration arm, but side effects correlated with the time of peak serum levels in most patients (data not given). AP treatment was not associated with any change in vital signs including body temperature (data not given).

Efficacy. The results of quantitative tests of visual and motor function are summarized in table 2. Six patients had baseline abnormalities in contrast

Table 2. Summary of efficacy test results

Efficacy end point	Treatment arm		
	Placebo	Low	High
Visual testing			
Mean contrast sensitivity*	1.25 ± 0.06†	1.38 ± 0.06‡	1.40 ± 0.04‡
Mean flicker fusion frequency (cps)	29.3 ± 1.6	32.6 ± 2.1	29.4 ± 0.8
Mean P100 latency (msec)	142 ± 8	141 ± 9	140 ± 8
Quantitative motor testing			
Hamstring strength (dynes/m²)	102 ± 18	108 ± 19	107 ± 20
Quadriceps strength (dynes/m²)	145 ± 32	158 ± 29	153 ± 30
Neurologic examination			
Strength score§	74 ± 5	75 ± 5	76 ± 5¶
Videotape score#	120 ± 23	126 ± 21¶	127 ± 27**

* Log threshold contrast level.
† Mean ± standard error.
‡ Statistically significantly improved compared with the placebo arm ($p = 0.05$, Wilcoxon signed rank test).
§ Total leg-strength score was the sum of individual scores on the MRC scale[18] for strength of the hamstrings and of the iliopsoas, quadriceps, and anterior tibialis muscles.
¶ Statistically significantly improved compared with the placebo arm ($p = 0.016$, Wilcoxon signed rank test).
# Videotaped examination score was the sum of scores given by a blinded reviewer of leg strength and spasticity and of ambulation ability.
** Statistically significantly improved compared with the placebo arm ($p = 0.02$, Wilcoxon signed rank test).

Table 3. Results of contrast sensitivity testing

Pt no.	Eye	Contrast sensitivity (log threshold contrast level)		
		Placebo	Low	High
1	OD	1.05	1.20	1.35
	OS	1.20	1.20	1.35
2	OS	1.50	1.35	ND
3	OS	1.20	1.35	1.20
5	OD	1.05	1.35	1.35
	OS	1.05	1.35	1.35
6	OD	1.35	1.65	1.50
	OS	1.35	1.65	1.50
8	OS	1.35	1.50	1.35
Mean ± SE		1.25 ± 0.06	1.38 ± 0.06*	1.40 ± 0.04*

* Improvement compared with placebo ($p = 0.05$, Wilcoxon signed rank test).

sensitivity in at least one eye (table 3). Of nine eyes tested, five improved during both the low- and high-concentration arms, three improved during only one active treatment arm, and only one eye worsened on treatment. A statistically significant improvement was seen in mean contrast sensitivity both low and high serum concentrations (table

Mean flicker fusion frequencies and mean P100 latencies showed slight improvement on treatment, but the differences were not statistically significant (data not given).

Table 4. Leg-strength scores on neurologic examination and videotaped examination score

Pt no.	Total leg-strength score*			Videotaped examination score†		
	Placebo	Low	High	Placebo	Low	High
1	88	88	90	139	159	162
2	82	80	ND	137	143	ND
3	62	59	65	147	152	170
4	78	76	82	167	150	177
5	89	89	89	158	152	148
6	55	62	59	13	38	25
7	52	56	58	21	26	25
8	83	88	87	175	189	183
Mean ± SE	73 ± 5	75 ± 4	76 ± 5‡	120 ± 23	126 ± 21‡	127 ± 27§

* Total leg-strength score was the sum of individual scores on the MRC scale[18] for strength of the hamstrings and of the iliopsoas, quadriceps, and anterior tibialis muscles.
† Videotaped examination score was the sum of scores given by a blinded reviewer of leg strength and spasticity and of ambulation ability.
‡ Significantly increased compared with placebo ($p = 0.016$, Wilcoxon signed rank test).
§ Significantly increased compared with placebo ($p = 0.02$, Wilcoxon signed rank test).

Improvements were seen in lower extremity strength on neurologic examination and in ratings of videotapes of the lower extremity examination (table 4). Total leg-strength score improved during both treatment arms in three patients, and during only the high-concentration arm in three patients. The score decreased during the low-concentration arm in three patients. The mean total leg-strength score improved significantly during the high-concentration arm compared with the placebo arm (table 4). Scores of blinded ratings of videotaped examinations of the lower extremities improved during both treatment arms in five of seven patients. Scores worsened in both treatment arms in one patient. Mean scores significantly improved compared with the placebo arm during both the low- and high-serum-concentration arms (table 4). Quantitative testing of quadriceps and hamstrings showed small, statistically insignificant increases in mean strength (table 2). No changes were seen in AI or EDSS scores (data not given).

Discussion. We found rates of treatment-related improvements in visual and lower extremity motor function that were similar to those reported in previous short-term trials of AP. Jones et al[6] treated five patients with labile visual symptoms in an open-label trial and noted improvement in vision testing in all. Stefoski et al[7] studied intravenously administered AP in a blinded placebo-controlled trial in 12 temperature-sensitive MS patients and reported significant improvement of specific neurologic deficits in 10 patients. In a trial of short-term oral AP treatment, Davis et al[8] treated 20 temperature-sensitive MS patients in a placebo-controlled format and reported mild to moderate improvement of either visual or motor symptoms in all of the 15 patients who received AP and none of the five patients who received placebo. Recently, the same group reported a double-blind, placebo-con-

trolled trial of oral AP with treatment durations of up to 5 days.[9] Thirteen of 17 MS patients improved on AP and only three of nine patients improved on placebo. These studies suggest that AP may induce improvements in specific neurologic deficits in MS patients, but the studies were limited by questions about blinding, failure to randomize treatment, and failure to either use prospectively defined neurologic deficits or adjust significance levels to compensate for multiple comparisons.

A recently reported randomized, double-blind, placebo-controlled, crossover trial of AP[10] addressed some of the design weaknesses in earlier studies and suggested that not only can AP treatment improve specific residual deficits, but it can also improve overall function. In 68 patients receiving escalating oral doses of AP over 3 months, the mean EDSS score improved by 0.28 with treatment. Ten patients improved by one point or more in the EDSS score on AP treatment and only three worsened, whereas no patient improved by that much on placebo and 11 worsened. Whereas improvements on quantitative tests for vision and oculomotor function correlated with serum AP levels in individual patients,[11] overall neurologic improvement did not.[10] Although the escalating dose format could have unblinded patients and examiners, these results are the most convincing to date that AP treatment can lead to functionally significant improvement in residual deficits in MS patients.

Testing in the present trial utilized measures that yielded quantitative results (flicker fusion frequency, contrast sensitivity, VERs, and quantitative determinations of quadriceps and hamstring strength) to allow the detection of a serum concentration-response relationship. Although the response rates showed a slight but statistically insignificant serum concentration relationship, the magnitude of response was not serum concentration-related for any of the measures employed. We may have used too few patients and serum concentrations to detect differences. The serum concentration-response curve for AP may plateau at high concentrations, and we may have chosen two serum concentration ranges that were on the plateau. The lower serum concentration range of 30 to 59 ng/ml may therefore be adequate for inducing improvement of some neurologic deficits.

The frequency of paresthesias and dizziness in the high-serum-concentration arm is similar to that in other trials. Stefoski et al[7] reported paresthesias in 12 of 12 patients treated with intravenous AP and five of 15 patients on oral AP, and van Diemen et al[10] reported paresthesias in 15 of 68 patients on oral AP. Jones et al[6] found dose-limiting dizziness and disorientation in five chronic MS patients. Stefoski et al reported dizziness and gait imbalance in five of 12 patients receiving intravenous AP[7] and in 13 of 17 patients on oral AP.[9] Van Diemen et al[10] reported dizziness in 36 of 68 patients.

There are no previous reports of seizures or episodes of confusion in MS patients on AP. Intravenous AP induces seizures in mice,[22] and seizures occurred in patients receiving AP treatment for botulism,[23] myasthenia gravis,[24] and Lambert-Eaton syndrome.[24] No seizures occurred during 3 months of AP treatment in 68 patients,[10] but seizures occurred in two patients from that study who continued open-label treatment (C. Polman, personal communication). There are no previous reports of serum levels at the time of AP-induced seizures, but serum levels greater than 100 ng/ml have been reported in patients without seizures (reference 11; F. Davis, personal communication). Because the high-serum-concentration arm produced much greater toxicity than the low without any obvious therapeutic advantage, it seems likely that clinically useful serum concentrations would be in the 30 to 59 ng/ml range.

The present study was limited by a small sample size and short treatment duration. The sample size was based on the crossover design, the use of concentration control, and the reported rates of improvement in previous trials. Eight patients randomized to three arms are equivalent to 24 patients in a three-arm parallel design trial.[25] Interpatient variability is minimized because in a crossover trial each patient serves as his or her own control.[25] Variability is further reduced by serum concentration control. The observed response rate was similar to the 80% improvement rate seen by others.[7-9] The short treatment duration employed in this trial was based on previous reports of responses with similar or shorter treatment durations.[7,8] We calculated the minimum time necessary to achieve a pharmacokinetic steady state in all patients. Other studies found that side effects are greatest when drug treatment is started and then decrease with duration of treatment,[10] so our patients may have experienced maximal side effects for the serum concentration used. The latter limitation may have contributed to the lack of improvement in overall function (EDSS and AI scores).

This trial demonstrates that a new methodology, concentration control, can be usefully applied to the assessment of some drug treatment effects in MS. The use of concentration control methodology in clinical trials was first proposed by Sanathanan and Peck,[12] based on the development of techniques to predict an individual's pharmacokinetic response from population pharmacokinetic characteristics.[16] This allows dosage adjustments to be made in patients in real time in response to serum concentration measurements. This methodology, successfully applied to the study of the antineoplastic agent suramin,[26] appears to be applicable to neurologic diseases as well.

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The Effect of 4-Aminopyridine on Clinical Signs in Multiple Sclerosis: A Randomized, Placebo-Controlled, Double-Blind, Cross-over Study

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To find out whether treatment with 4-aminopyridine is beneficial in multiple sclerosis (MS), 70 patients with definite MS entered into a randomized, double-blind, placebo-controlled, cross-over trial in which they were treated with 4-aminopyridine and placebo for 12 weeks each (maximum dose, 0.5 mg/kg of body weight). The estimated effect of the treatment as measured with the Kurtzke expanded disability status scale, which was the main evaluation parameter, was 0.28 point ($p = 0.001$). A significant decrease in the scale score (1.0 point or more) was encountered in 10 patients (16.4%) during oral treatment with 4-aminopyridine whereas it was not seen during placebo treatment ($p < 0.05$). A significant subjective improvement (defined as an improvement that significantly affected the activities of normal daily life) was indicated by 18 patients (29.5%) during 4-aminopyridine treatment and by 1 patient (1.6%) during placebo treatment ($p < 0.05$). Significant improvements related to 4-aminopyridine occurred in a number of neurophysiological parameters. No serious side effects were encountered. However, subjective side effects such as paresthesias, dizziness, and light-headedness were frequently reported during 4-aminopyridine treatment. Analysis of subgroups revealed that there was no difference in efficacy between those patients randomized to receive 4-aminopyridine and then placebo and those randomized to receive placebo and then 4-aminopyridine or between patients with and those without subjective side effects. Especially patients with temperature-sensitive symptoms and patients characterized by having longer duration of the disease and being in a progressive phase of the disease were likely to show clear clinical benefit.

van Diemen HAM, Polman CH, van Dongen TMMM, van Loenen AC, Nauta JJP, Taphoorn MJB, van Walbeek HK, Koetsier JC. The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study. Ann Neurol 1992;32:123–130

In a small number of studies, the potassium channel blocker 4-aminopyridine (4-AP) demonstrated an ability to induce a transient improvement in clinical signs and symtoms in patients with multiple sclerosis (MS) [1–4]. These favorable effects probably are due to the restoration of nerve conduction in demyelinated nerve fibers by prolongation of the repolarization phase of the action potential [5–7].

Although remarkable improvements were reported, especially concerning motor and visual functions, definite conclusions cannot be drawn from these studies since the drug was given for a very short period to small groups of highly selected patients. Most of the studies either were not randomized or not controlled, or used uncommon outcome criteria.

In this study, we present the results of the first randomized, double-blind, placebo-controlled, cross-over study with long-term oral administration of 4-AP in patients with MS. The effect of 4-AP on the clinical signs in MS was investigated in 70 patients with clinically definite or laboratory-supported definite MS according to the criteria of Poser and associates [8].

Patients and Methods

Selection of Patients

The inclusion criteria were definite MS [8], a Kurtzke expanded disability status scale (EDSS) score at entry of 2.0 to 7.5 points [9], and an age between 18 and 70 years.

Exclusion criteria were a recent relapse, concomitant diseases confusing or mimicking the picture of MS, and a medi-

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cal history of epileptic fits or cardiac, hepatic, or renal disease. Pregnant women or women of childbearing age not using an effective method of birth control were also excluded as were patients who used any other medication having a stimulating effect on neurotransmitter release. Before entry into the study, electrocardiography (ECG) and blood examinations (hematology, liver and renal function) were performed. Patients with abnormalities were not eligible for the study.

Informed consent was obtained from all patients before being accepted into the study. The protocol was approved by the Ethical Committee of the Free University Hospital, Amsterdam.

Treatment

4-AP capsules (5 mg and 10 mg) and placebo capsules (Avicel) were prepared by the hospital pharmaceutical department. All patients were treated with both 4-AP and placebo for 12 weeks, each according to a randomized, bouble-blind, cross-over study design. There was no wash out between the first and the second treatment period. Patients were examined at the outpatient clinic (Free University Hospital, Amsterdam) at the start of the treatment (week 0) and at weeks 2, 6, 12 (cross-over), 14, 18, and 24. The starting dose for both treatment periods was 10 to 15 mg/day in two to three divided doses, which was elevated with 5 to 15 mg/day at weeks 2 and 6, respectively, and weeks 14 and 18 up to a maximum dose of 0.5 mg/kg of body weight. The doses of 4-AP and placebo were determined on the basis of occurring effects or side effects. Compliance of the patients was controlled by counting capsules and measuring 4-AP serum levels.

Assessment

Clinical assessments were made by means of the EDSS and the functional systems (FS) [9]. In order to prevent interrater variability, all patients were examined by the same blinded physician (*H. A. M. v. D.*) during the course of the study. The EDSS and FS scores were obtained at weeks 0, 2, 6, 12, 14, 18, and 24.

Visual acuity (VA) and contrast sensitivity (CS) measurements were used to evaluate the optic function. VA was measured using the Snellen chart. CS was measured using the contrast sensitivity test chart (VCTS 6500 [Vistech Consultants, Inc, Dayton, OH]), as described in detail elsewhere [10, 11]. VA and CS were measured before the start of treatment and at the end of the first and second treatment periods.

All side effects or concomitant diseases that were encountered by the patient were registered. Relapses were documented.

To evaluate the subjective response of the patients, a 5-point nominal scale ranging from + + to − − was used. The patient was asked to indicate 0 in case of no change, + or − in case of a slight improvement or deterioration, and + + or − − in case of a significant improvement or deterioration, respectively. Significant improvement or deterioration was defined as an improvement or deterioration that significantly affected the activities of normal daily life. Subjective responses were registered at the end of the first and the second treatment period. After the first treatment period, the response of the patient was based on a subjective difference between week 0 and week 12. After the second treatment period, the response of the patient was based on the subjective difference between week 12 and week 24.

As neurophysiological parameters, visual evoked potentials (VEPs) and eye movement registrations (EMRs) were determined and electroencephalography (EEGs) performed. A detailed description of the used registration techniques for VEPs and EMRs in our laboratory was given by van Dongen and coauthors [12]. These registrations were performed before the start of the treatment and at the end of the first and second treatment periods. Evaluation parameters were latency and amplitude of the P100 peak for the VEP and saccadic latency, peak velocities of eye movements, and smooth pursuit gain of the critical frequency for the EMR. The EEGs were recorded on a 16-channel Siemens Elema machine (Siemens Elema AB, Solma, Sweden) using the international 10-20 system of electrode placement with referential, source, and bipolar montages (bandwith, −3 dB: 0.26–30.00 Hz). Hyperventilation and photic stimulation were done routinely during recording of at least 20 minutes. The EEGs were recorded before the start of the treatment and after 2 weeks of each treatment period. The EEGs were scored by conventional visual inspection by an experienced neurophysiologist who was aware of the study protocol but unaware of the clinical history of the patient and the medication used.

Blood studies (hemoglobin, white blood cell count, platelets, urea, creatinine, total protein, alkaline phosphatase [AF], serum glutamic-oxaloacetic [SGOT], and glutamic-pyruvic transaminases [SGPT], gamma-gamma-glutamyltransferase, Na^+, and K^+) were performed before entry into the study and at weeks 2, 12, 14, and 24.

Efficacy Parameters

At the start of the trial, we decided that the primary analysis would involve a comparison of the EDSS scores. Both the numbers of patients showing a significant EDSS change (1.0 point or more [13–15]) and the mean changes in EDSS scores at the end of both treatment periods were to be evaluated. Secondary evaluation parameters were the subjective responses as indicated by the patient, the FS, the number of relapses, the results of the measurements of optic function, and the results of VEPs and EMRs.

Responders to 4-AP were defined as patients with either a decrease of the EDSS of 1.0 point or more or a significant positive subjective response during the treatment period with 4-AP.

Preference and Prediction

At the end of the study, patients were asked to indicate during which period of treatment they felt better (preference) and during which period they thought 4-AP was administered (prediction).

Withdrawals

Patients were allowed to withdraw from the study at any time, for example, of their own free will or due to side effects of the tested drugs. Patients in whom, because of severe progression of signs and symptoms, treatment with high-dose

intravenous methylprednisolone (Solu-Medrol, 5 × 500 mg) was installed were withdrawn from the study at the moment of the initiation of the steroid administration, since the data to be obtained after this moment were believed to be highly influenced by the steroid treatment.

Side effects and/or toxicity were evaluated in all patients who entered the study. If patients withdrew from the study during the first period (i.e., before the cross-over) and therefore did not enter the second period, only the side effects during the first treatment period could be considered. If patients withdrew during the second period, the side effects of both periods were evaluated.

The analyses of efficacy were performed only in those patients who completed at least 2 weeks of a treatment period. This means that if patients withdrew from the study during the first 2 weeks of the first period, efficacy was not evaluated. If patients withdrew from the study during the first period after at least 2 weeks of treatment, efficacy was analyzed for this period based on the data obtained during the last visit for which the patient was still receiving treatment. If patients withdrew from the study during the first 2 weeks of the second period, only the efficacy results of the first period were analyzed. If patients withdrew from the study during the second period after at least 2 weeks of treatment, efficacy was analyzed for both periods. Analyses for the second period were based on the data obtained during the last visit for which the patient still was receiving treatment.

Statistical Analysis

Because of the cross-over design, in order to interpret correctly the results of the second treatment period, it was necessary to investigate whether or not the responses observed during this period were influenced by the medication given in the first period. Thus, we investigated whether there was any residual effect of 4-AP that persisted from the first to the second period. To test hypotheses of zero residual effect of 4-AP, for each response variable separately, the sums of the response for the first and second treatment periods were compared between the two treatment-order groups by means of the two-sample t test or Wilcoxon's rank-sum test (in case of nonnormality). Following the recommendation of Grizzle [16], the hypothesis of zero residual effect was tested at a significance level of 10%. In the absence of a residual effect of 4-AP, to investigate the effect of 4-AP, the following method was used: Taking each variable separately, for each subject the response observed at the first treatment period was subtracted from that observed at the second period. The sampling distribution for the 4-AP/placebo treatment-order group reflected the systematic deviation of 4-AP over placebo, whereas the sampling distribution for the other treatment-order group reflected this same deviation with the opposite sign. The hypothesis of no effect of 4-AP implies that the sampling distributions of the two treatment-order groups are the same. Hypotheses of no effect were tested two-sided at a significance level of 5%, using either two-sample t tests or Wilcoxon's rank-sum tests. If for a given variable, there was evidence for a residual effect of 4-AP, the analysis was restricted to the data of the first treatment period, in which case the responses in the placebo and 4-AP treatment groups were compared by either two-sample t tests or Wilcoxon's rank-sum tests.

The method of analysis of side effects was similar to the method outlined above, except that responses are binary (present or not present) rather than semiquantitative or quantitative. A discussion of the analysis of binary data in the context of cross-over trials was given by Fleiss [17].

The dependency of being a responder on patients' characteristics was tested using chi-square tests or Mantel's test for a trend in a proportion. To study the influence of such characteristics, simultaneously logistic regression was used.

Results

Patient Population

Seventy patients, 43 women and 27 men, entered the trial. Their age ranged from 23 to 68 years (mean, 41.6 years; median, 41.0 years). The duration of disease ranged from 2 months to 25 years (mean, 86 months; median, 72 months). The mean EDSS score was 5.0 (median, 5.5). A chronic progressive form of MS was present in 52 patients (74.3%). Eighteen patients (25.7%) had a relapsing-remitting form of the disease. Based on anamnestic information, 67% of the patients were temperature sensitive and 23% were not (10% not clear).

Medication

The mean daily dose of 4-AP administered at the end of the treatment period was 31.2 mg (range, 10–50 mg, divided in two–four doses). The 4-AP dose per kilogram of body weight ranged from 0.17 to 0.55 mg.

Withdrawals

One patient who was randomized withdrew from the study before taking any medication.

During the first treatment period, which was entered by 69 patients, there were 6 withdrawals. Two patients withdrew during the first week of the 4-AP treatment (1 due to subjective side effects, 1 due to a stomatitis), 1 patient withdrew after 4 weeks of 4-AP administration because of obstipation, and 3 patients (2 during placebo and 1 during 4-AP) were withdrawn from the study between week 6 and week 12 because of a deterioration of their clinical neurological status for which intravenous methylprednisolone was given. Subjective side effects and toxicity during the first treatment period were evaluated for all 69 patients who entered it (34 receiving 4-AP, 35 receiving placebo). The evaluation of efficacy data was performed for the 67 patients (32 receiving 4-AP, 35 receiving placebo) who completed at least 2 weeks of treatment.

After the cross-over during the second treatment period, which was entered by 63 patients, there were 6 withdrawals. One patient withdrew within the first week of the 4-AP treatment because of subjective side effects, 2 patients withdrew between weeks 18 and 24 due to subjective side effects (1 patient on 4-AP and 1 patient on placebo treatment), and 3 patients were

withdrawn from the study between weeks 14 and 18 (all placebo) because of a deterioration of the clinical neurological status for which they were treated with intravenous methylprednisolone. All 63 patients were evaluated for side effects during the second treatment period (33 receiving 4-AP, 30 receiving placebo). Efficacy parameters were analyzed for those 62 patients (32 receiving 4-AP, 30 receiving placebo) who finished at least 2 weeks of treatment during this period.

In summary, a total of 6 patients withdrew because of side effects (5 on 4-AP, 1 on placebo) and 6 patients were withdrawn because of intravenous steroid treatment (5 on placebo, 1 on 4-AP). A total of 57 patients completed the study protocol.

Assessment of Efficacy

There was a statistically significant estimated effect of 4-AP on the mean EDSS score after 2, 6, and 12 weeks of treatment, as is shown in Table 1. As shown in Table 2, the significant effect on the mean EDSS score holds for the patient group that was first treated with 4-AP as well as for the patient group that was first treated with placebo. In Table 3, the changes in EDSS scores per treatment period are indicated for all patients; there was a significant difference in favor of 4-AP treatment ($p < 0.05$). This table illustrates that there was a significant improvement on the EDSS in 10 patients during the 4-AP period whereas this did not occur during the placebo period. A significant increase of the EDSS score was registered in 3 patients during the 4-AP period and in 11 patients during placebo treatment.

In Table 4, the total number of subjective improvements/deteriorations during the 4-AP and placebo treatment periods as reported by the patients is shown. A significant improvement was reported by 18 patients during 4-AP treatment and by 1 patient during placebo treatment, whereas a significant deterioration was reported by 2 patients during 4-AP treatment and by 15 patients during placebo treatment ($p < 0.05$).

Concerning the FS, a significant improvement was found for the pyramidal functions ($p < 0.01$) after the period with 4-AP treatment. No significant changes were registered for the cerebellar, brainstem, sensory, bladder and bowel, and cerebral functions.

There were no statistically significant changes in the optic function, as measured with the VA and CS (Table 5).

Table 1. Estimated Effects of Orally Administered 4-Aminopyridine (4-AP) on the Expanded Disability Status Scale (EDSS)

Response Variable	Estimated Effect of 4-AP	95% Confidence Interval	*p* Value
EDSS (after 2 wk)	−0.15	(−0.29, −0.00)	0.043
EDSS (after 6 wk)	−0.24	(−0.38, −0.10)	0.001
EDSS (after 12 wk)	−0.28	(−0.41, −0.16)	0.0001

Table 2. The Mean Expanded Disability Status Scale (EDSS) Score and the Mean Change in EDSS (ΔEDSS) after Treatment[a]

	Weeks						
	0	2	6	12	14	18	24
Placebo/4-AP patient group							
Mean EDSS	4.86	4.91	5.04	5.01	5.06	4.90	4.92
ΔEDSS			+ 0.15			− 0.09	
4-AP/Placebo patient group							
Mean EDSS	5.26	5.18	5.15	5.08	5.25	5.32	5.31
ΔEDSS			− 0.18			+ 0.23	

[a]Week 0 = start of treatment, week 12 = cross-over time
4-AP = 4-aminopyridine

Table 3. Changes in the Expanded Disability Status Scale[a]

	4-AP Treatment Period				
	⇓	Unchanged	⇑	Dropout	Total
Placebo treatment period					
⇓	0	0	0	0	0
Unchanged	6	43	2	2	53
⇑	4	6	0	1	11
Dropout	0	2	1	3	6
Total	10	51	3	6	70

[a]For all patients, the change during both treatment periods can be derived from the table. Bold numbers indicate the numbers of patients with a significant change.

⇓ = a decrease in EDSS of 1 point or more; ⇑ = an increase in EDSS of 1 point or more; Unchanged = a change in EDSS of less than 1 point; 4-AP = 4-aminopyridine.

Table 4. Subjective Responses[a]

	4-AP Treatment Period				
	− +	+/0/−	− −	Missing	Total
Placebo treatment period					
+ +	0	1	0	0	1
+/0/−	11	36	1	1	49
− −	7	6	0	2	15
Missing	0	1	1	3	5
Total	18	44	2	6	70

[a]For all patients, the change during both treatment periods can be derived from the table. Bold numbers indicate the numbers of patients with a significant change.
+ + = significant improvement; +/0/− = no significant changes; − − = significant impairment; 4-AP = 4-aminopyridine.

Table 5. Estimated Effects of Orally Administered 4-Aminopyridine (4-AP) on Optic Function and Neurophysiological tests

Response Variable	Estimated Effect of 4-AP	95% Confidence Interval	*p* Value
Visual acuity[a]			
OD	—	—	0.058
OS	—	—	0.399
Contrast sensivity			
OD	0.26	(−0.56, 1.07)	0.531
OS	−0.07	(−0.95, 0.81)	0.871
Visual evoked potential			
Latency (msec) OD	−3.86	(−6.97, −0.75)	0.017
Amplitude (μV) OD	0.58	(−0.08, 1.25)	0.088
Latency (msec) OS	−3.76	(−7.13, −0.39)	0.030
Amplitude (μV) OS	−0.28	(−1.07, 0.51)	0.486
Eye movement registration			
Smooth pursuit eye movement			
Gain[b]	0.14	(0.06, 0.23)	0.001
Saccadic eye movement			
Latency (msec) OD	−1.95	(−7.76, 3.87)	0.506
Vmax (d/s) OD abd	21.65	(−1.50, 44.80)	0.068
Vmax (d/s) OS abd	28.99	(−6.80, 64.77)	0.113
Vmax (d/s) OD add[b]	77.50	(137.1, 141.29)	0.019
Vmax (d/s) OS add[b]	131.38	(57.15, 205.60)	0.001

[a]Based on Wilcoxon's rank-sum test because of nonnormal data.
[b]Based on the response of the first treatment period because of a residual effect of 4-aminopyridine ($p < 0.05$).
OD = right eye; OS = left eye; Vmax = peak velocity; add = adducting; abd = abducting; d/s = degrees second.

Relapses occurred in 1 patient during 4-AP treatment and in 4 patients during placebo treatment.

The results of the neurophysiological assessment are summarized in Table 5. A statistically significant effect of 4-AP was found for the VEP latencies of both eyes, while there was no significant change in VEP amplitude. The EMR showed a statistically significant effect for the smooth pursuit gain and the adduction peak velocities of both eyes.

Side Effects and Toxicity

Side effects (Table 6) were experienced during both treatment periods by 10 patients and during one of both by 44 patients (6 during placebo and 38 during 4-AP treatment, $p < 0.0001$). In general, these subjective side effects were reported to be mild, although 14 patients (all on 4-AP treatment) needed a dose reduction and 4 patients (3 on 4-AP, 1 on placebo) withdrew from the study because of subjective side effects. Most patients reported these side effects to occur 30 to 45 minutes after taking the medication, while they generally resolved within 2 to 5 hours.

A number of incidental illnesses were observed. During the 4-AP treatment phase, the diagnoses were cystitis (2 patients), stomatitis (1 patient), transient urticaria (1 patient), fracture of a metacarpal bone (1 patient), and ankle distorsion (1 patient). During the placebo treatment, the diagnoses were cystitis (1 patient), angina of the throat (1 patient), deep venous thrombo-

Table 6. Subjective Side Effects (Combinations within Patients Did Occur)

Subjective Side Effects	No. of Patients during 4-AP Period	No. of Patients during Placebo Period
Total no. of patients with side effects	48	16
Paresthesias and dysesthesias (perioral, hands and feet)	15	10
Dizziness (light-headedness)	36	4
Gait instability	11	1
Nausea (and vomiting)	9	—
Restlessness and anxiety	4	—
Abdominal pain	5	—
Obstipation	1	—
Headache	—	1

4-AP = 4-aminopyridine

sis in the leg (1 patient), and a fracture of the collum of the hip (1 patient). In all these patients, the reaction to the installed treatment was appropriate.

No epileptic fits were encountered. In 2 patients, significant changes in the EEG were found. In 1 patient generalized spikes and spike waves were recorded during 4-AP treatment and in 1 a significant increase in temporal slow-wave activity was observed during placebo treatment.

The blood tests did not show any significant effects of 4-AP on the hematological, renal, and hepatic parameters or the electrolytes (all data, $p > 0.05$). Abnormal values in individual patients were always clinically irrelevant and transient without requiring changes in the treatment protocol.

Preference and Prediction

Of the 62 patients who were able to compare the efficacy in both periods, 20 did not have a preference. Thirty-one patients preferred the 4-AP period and 11 preferred the placebo period ($p < 0.01$). Forty-six patients (out of 62) thought that they were able to predict in which of the two oral treatment periods 4-AP was given. For 41 patients, this prediction was correct and for 5 it was not ($p < 0.0001$).

Responders to 4-Aminopyridine

Eighteen patients (29.5%) were characterized as being responders to 4-AP. The percentages of responders in patients with and patients without subjective side effects during the 4-AP period were respectively, 35.5% and 33.3% ($p = 1.0$). Patients with side effects during both treatment periods were excluded from this analysis.

Differences in patient characteristics between the responders and the nonresponders to 4-AP were found for a number of variables. Significantly more responders had a longer duration of disease (response rates rising from 7% for patients with a disease duration < 3 years to 46% for patients with a disease duration > 10 years, $p < 0.05$), had increased EDSS scores (response rates rising from 0 in patients with an EDSS score ≤ 3.5 to 42% in patients with an EDSS score ≥ 5.5, $p = 0.01$), had increased pyramidal function on the FS ($p < 0.05$), were in a chronic progressive form of the disease as compared to a relapsing-remitting form (response rates 37% and 7%, respectively, $p < 0.05$), and were temperature sensitive as compared to nontemperature sensitive (response rates of 38% and 13%, respectively, $p < 0.05$). No significant differences were found for age ($p = 0.076$); sex ($p = 0.852$); age of onset ($p = 0.829$); progression coefficient ($p = 0.175$); and cerebellar ($p = 1.0$), brainstem ($p = 0.348$), sensory ($p = 0.799$), and bladder and bowel ($p = 0.672$) functions on the FS. Using logistic regression, the "duration of the disease" and the "temperature sensitivity of symptoms" were the most important prognostic factors.

Discussion

The results of this randomized, double-blind, placebo-controlled, cross-over study, in which the EDSS was the main evaluation parameter, demonstrate that 4-AP is superior to placebo and has a favorable effect on the disability of MS patients.

A significant difference concerning the mean EDSS score of 0.28 point was found in favor of the 4-AP period compared to the placebo period. This difference occurred irrespective of the cross-over design of the trial, as shown in Table 2. In both the placebo/4-AP and the 4-AP/placebo patient groups, the EDSS score decreased during 4-AP and increased during placebo treatment.

Since changes in the EDSS are not of equal importance over its whole range and since a difference of 0.28 EDSS point is clinically irrelevant (the smallest change that the EDSS recognizes being 0.5 point), it might be more appropriate to analyze the number of patients that showed a change of 1.0 point or more on the EDSS. Most experts agree that a change of at least 1.0 point represents a significant change in the context of a clinical trial, this change being indicative of an important change in the disability of an MS patient expressing, for example, between EDSS scores 5.0 and 6.0 the requirement of constant assistance (cane, crutch, brace) to walk 100 to 200 m and between EDSS scores 6.0 and 7.0 the difference between being able to walk (although requiring assistance) and being essentially restricted to a wheelchair [9, 13–15]. A significant decrease in EDSS scores was seen in 10 patients (16.4%) during 4-AP treatment whereas it was not seen during placebo treatment. A significant increase in EDSS score was seen in 3 patients (4.9%) during the 4-AP period and in 11 patients (18%) during the placebo period. Of course, these data are influenced by the cross-over design of the study, since, for example, in 4 patients an improvement during 4-AP treatment in the first period was followed by a deterioration during placebo treatment in the second period (probably related to 4-AP withdrawal). Because of the short duration of each treatment period and because of the cross-over design, we refrained from analyzing the time to reach a significant change.

Our data confirm the conclusion of Davis and colleagues [3] and Stefoski and associates [4] that orally administered 4-AP can produce clinically important improvements in MS patients, although the percentage of patients showing significant improvement is much lower in our study. This might at least in part be due to the fact that these authors used a rather uncommon way to assess the grade of neurological dysfunction. Motor function, vision, and oculomotor function were

A. INGREDIENT NAME:

BETAHISTINE DIHYDROCHLORIDE

B. Chemical Name:

N-Methyl-2-(2-pyridyl)ethylamine dihydrochloride

C. Common Name:

Ger., Egypt, Greece, Neth, Switz, U. K. Serc. *See file for various names in different countries.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Quality Assay Tot. base (%): 98.965

E. Information about how the ingredient is supplied:

White to off white crystals, is odorless, crystals obtain from alcohol

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Seipel, J. H. and Meyer, J. S. Dementia. *J Clin.,I Pharm.* 1975;15: 144 & 1974; 14: 280.

Tighilet, B., Leonard, J. and Lacour, M. Betahistine dihydrochloride treatment facilitates vestibular compensation in the cat. *Journal of Vestibular Research,* 1995; 5(1): 53-66.

Oostervald, W. J. Betahistine dihydrochloride in the treatment of vertigo of peripheral vestibular origin. A double-blind placebo-controlled study. *Journal of Laryngology & Otology.* 1984; 98(1): 37-41.

Petermann, W. and Mulch, G. Long-term therapy of Meniere's disease. Comparison of the effects of betahistine dihydrochloride and hydrochlorothiazide. *Fortschritte der Medizin*, 1982; 100(10): 431-435.

Fraysse, B., Bebear, J. P., and Dubreiul, C. Betahistine dihydrochloride versus flunarizine. A double-blind study on recurrent vertigo with or without cochlear syndrome typical of Meniere's disease. *Acta Oto-Laryngologica*, 1991: 490 (Suppl): 1-10.

Pfaltz, C. R. and Aoyagi, M. Calcium-entry blocker in the treatment of vestibular disorders. *Acta Oto-Laryngologica*, 1988; 460 (Suppl): 135-142.

Oosterveld, W. J. Efect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study. *Clinical Otolaryngology*, 1987; 12(2): 131-135.

H. Information about dosage forms used:

Scored tablets

I. Information about strength:

4mg in Canada
8mg in U. K.

J. Information about route of administration:

Orally

K. Stability data:

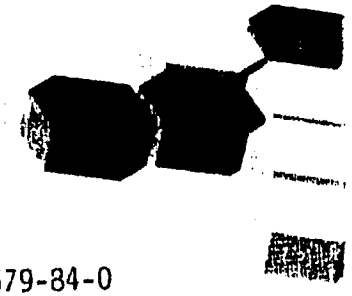
Melting point: 152° C to 154 C
Incompatibilities:
- Acids
- Acid Chlorides
- Acid Anhydrides
- Oxidizing Agents

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1882
H52803



General Product Data

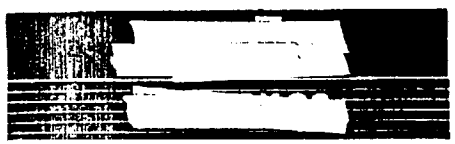
CAS No	:	5579-84-0
FW	:	209.12
Molecular formula	:	C8 H12 N2 . 2 H Cl

Lot Specific Data

Appearance	:	NEARLY COLOURLESS CRYSTALLINE POWDER
Melting point ([C)	:	150[C
Quality assay Tot. base(%)	:	98.965
Loss/drying(%)	:	1.06
Heavy metals	:	<0.002 (NUMBER: %)
Additional	:	SOLUBILITY (2% IN WATER):CLEAR COLOURLESS SOLUTION, ASH:0.03% PH (2% SOLUTION):2.42, IRON<0.002%, ORGANIC IMPURITIES<0.5%
Manufacturing unit	:	899417

Product 16799.0000
Lot No. A0112613

2-(2-(METHYLAMINO)ETHYL)PYRIDINE
DIHYDROCHLORIDE 99%



Issued: 25-07-1997
A. Vanneste Quality Control Manager
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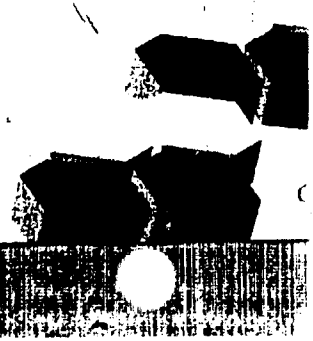


QUALITY CONTROL REPORT

CHEMICAL NAME.: BETAHISTINE DIHYDROCHLORIDE _____

MANUFACTURE LOT NO.: A011261301

PHYSICAL TEST

SPECICICATION TEST STANDARD.: USP__/NF__/MERCK__/BP__/COMPANY SPECS.___

1) DESCRIPTION.:
WHITE TO OFF WHITE CRYSTALS; IS ODORLESS, CRYSTALS OBTAIN FROM ALCOHOL.

2) SOLUBILITY.:
SOLUBLE IN WATER, IN ALCOHOL, AND IN CHLOROFORM.

3) MELTING POINT.:
MELTS AT ABOUT 148-149 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) SOLUTION RESPONDS TO THE TEST FOR CHLORIDE.

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

Use your web browser's "Back" key to return to previous topic.

MATERIAL SAFETY DATA SHEET

2-(2-(Methylamino)ethyl)pyridine dihydrochloride 99%
32311

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: 2-(2-(Methylamino)ethyl)pyridine dihydrochloride 99%

Company Identification: Acros Organics N.V.
One Reagent Lane
Fairlawn, NJ 07410
For information in North America, call: 800-ACROS-01
For emergencies in the US, call CHEMTREC: 800-424-9300
For emergencies in the US, call CHEMTREC: 800-424-9300

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
5579-84-0	2-(2-(methylamino)ethyl)pyridine dihydrochloride 99%	99	226-966-5

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Not available.
Appearance: faint yellow.
Not available.
Target Organs: None.

Potential Health Effects
The toxicological properties of this material have not been investigated. Use appropriate procedures to prevent opportunities for direct contact with the skin or eyes and to prevent inhalation.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:
Flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.
Skin:
Get medical aid. Flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes. Remove contaminated clothing and shoes.

Ingestion:
If victim is conscious and alert, give 2-4 cupfuls of milk or water. Get medical aid immediately.
Inhalation:
Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.
Notes to Physician:
Treat symptomatically and supportively.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:
As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. During a fire, irritating and highly toxic gases may be generated by thermal decomposition or combustion.
Extinguishing Media:
Use agent most appropriate to extinguish fire.
Autoignition Temperature: Not available.
Flash Point: Not available.
NFPA Rating: Not published.
Explosion Limits, Lower: Not available.
Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.
Spills/Leaks:
Clean up spills immediately, observing precautions in the Protective Equipment section.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:
Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Avoid contact with eyes, skin, and clothing. Avoid ingestion and inhalation.
Storage:
Store in a cool, dry place. Keep container closed when not in use.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:
Use process enclosure, local exhaust ventilation, or other engineering controls to control airborne levels.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
2-(2-(methylamino)ethyl)pyridine dihydrochloride 99%	none listed	none listed	none listed

OSHA Vacated PELs:
2-(2-(methylamino)ethyl)pyridine dihydrochloride 99%:
No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:
Wear chemical goggles.
Skin:
Wear appropriate protective gloves to prevent skin exposure.
Clothing:
Wear appropriate protective clothing to minimize

contact with skin.

Respirators:

A respiratory protection program that meets OSHA's 29 CFR ¦1910.134 and ANSI Z88.2 requirements must be followed whenever workplace conditions warrant a respirator's use.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State:	Not available.
Appearance:	faint yellow
Odor:	Not available.
pH:	Not available.
Vapor Pressure:	Not available.
Vapor Density:	Not available.
Evaporation Rate:	Not available.
Viscosity:	Not available.
Boiling Point:	@ 760.00mm Hg
Freezing/Melting Point:	152.00 - 154.00 deg C
Decomposition Temperature:	Not available.
Solubility:	Not available.
Specific Gravity/Density:	Not available.
Molecular Formula:	C8H12N2.2HCl
Molecular Weight:	209.12

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:
Stable under normal temperatures and pressures.
Conditions to Avoid:
Incompatible materials, strong oxidants.
Incompatibilities with Other Materials:
Not available.
Hazardous Decomposition Products:
Irritating and toxic fumes and gases.
Hazardous Polymerization: Not available.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
CAS# 5579-84-0 unlisted.
LD50/LC50:
Not available.
Carcinogenicity:
2-(2-(methylamino)ethyl)pyridine dihydrochloride 99% -
Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
RCRA D-Series Maximum Concentration of Contaminants: Not listed.
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
RCRA F-Series: Not listed.
RCRA P-Series: Not listed.
RCRA U-Series: Not listed.
Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
No information available
IMO
Not regulated as a hazardous material.
IATA
Not regulated as a hazardous material.
RID/ADR
Not regulated as a hazardous material.
Canadian TDG

No information available.

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL

TSCA

CAS# 5579-84-0 is not listed on the TSCA inventory.
It is for research and development use only.

Health & Safety Reporting List

None of the chemicals are on the Health & Safety Reporting List.

Chemical Test Rules

None of the chemicals in this product are under a Chemical Test Rule.

Section 12b

None of the chemicals are listed under TSCA Section 12b.

TSCA Significant New Use Rule

None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)

None of the chemicals in this material have an RQ.

Section 302 (TPQ)

None of the chemicals in this product have a TPQ.

Section 313

No chemicals are reportable under Section 313.

Clean Air Act:

This material does not contain any hazardous air pollutants.
This material does not contain any Class 1 Ozone depletors.
This material does not contain any Class 2 Ozone depletors.

Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.
None of the chemicals in this product are listed as Priority Pollutants under the CWA.
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

STATE

Not present on state lists from CA, PA, MN, MA, FL, or NJ.
California No Significant Risk Level:
None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: Not available.
Risk Phrases:
Safety Phrases:
S 24/25 Avoid contact with skin and eyes.

WGK (Water Danger/Protection)

CAS# 5579-84-0:

Canada

CAS# 5579-84-0 is listed on Canada's DSL/NDSL List.
WHMIS: Not available.
CAS# 5579-84-0 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 2/28/1995 Revision #2 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

Back to product information.

1211. Beryllium Hydride. BeH_2; mol wt 11.03. Be 81.72%, H 18.28%. Lower purity material prepd by treating dimethylberyllium with $LiAlH_4$ in ether: Barbaras *et al., J. Am. Chem. Soc.* **73**, 4585 (1951); higher purity by pyrolysis of di-*tert*-butylberyllium: Coates, Glocking, *J. Chem. Soc.* **1954**, 2526; Head *et al., J. Am. Chem. Soc.* **79**, 3687 (1957); from triphenyl phosphine and beryllium borohydride: Banford, Coates, *J. Chem. Soc.* **1964**, 5591.

White solid. Higher purity material is inert to laboratory air. Loss of hydrogen at 190-200° negligible, rapid at 220°. Reacts slowly with water, rapidly with dil acids. Insol in ether, toluene, isopentane. Reacts with diborane to form beryllium borohydride.

1212. Beryllium Hydroxide. BeH_2O_2; mol wt 43.03. Be 20.95%, H 4.69%, O 74.37%. $Be(OH)_2$. Prepn: Ehrlich in *Handbook of Preparative Inorganic Chemistry*, **vol. 1**, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 894.

Amorphous powder or crystals. d 1.92. Amphoteric. Very slightly sol in water and dil alkali. Sol in hot concd NaOH soln and acids.

USE: Manuf of beryllium and beryllium oxide.

1213. Beryllium Iodide. BeI_2; mol wt 262.82. Be 3.43%, I 96.57%. Prepn: Messerknecht, Biltz, *Z. Anorg. Chem.* **148**, 152 (1925); Ehrlich in *Handbook of Preparative Inorganic Chemistry*, **vol. 1**, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 892. Review of beryllium halides: Bell, *Advan. Inorg. Chem. Radiochem.* **14**, 255-332 (1972).

Needles, mp 480°, bp 488°. Very hygroscopic. Sublimes *in vacuo*. Reacts violently with water, giving off HI. Absorbs ammonia. Dissolves in alcohols, amines, with the formation of addition compds. *Keep tightly closed.*

1214. Beryllium Nitrate. BeN_2O_6; mol wt 133.02. Be 6.77%, N 21.06%, O 72.17%. $Be(NO_3)_2$. Prepn: *Gmelin's, Beryllium* (8th ed.) **26**, 102-104 (1930).

Trihydrate, white to slightly yellow, deliquesc cryst mass. mp ~60°. Very sol in water, alcohol. *Keep well closed in a cool place.* LD_{50} i.p. in guinea pigs: 50 mg/kg, *Handbook of Toxicology* **vol. 1**, W. S. Spector, Ed. (Saunders, Philadelphia, 1956) pp 46-47.

USE: Stiffening mantles in gas and acetylene lamps.

1215. Beryllium Nitride. Be_3N_2; mol wt 55.05. Be 49.11%, N 50.89%. Prepn: Ehrlich in *Handbook of Preparative Inorganic Chemistry*, **vol. 1**, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 898; Langsdorf, Jr., U.S. pat. **2,567,518** (1951 to USAEC).

White crystals to grayish white powder; mp 2200 ±40°. Volatile at bp, on further heating it dissociates into Be and N_2. Oxidized in air at 600°. Dec slowly by water, quickly by acids and alkalies with the evolution of ammonia.

1216. Beryllium Oxide. Beryllia. BeO; mol wt 25.01. Be 36.03%, O 63.97%. Prepn: *Gmelin's, Beryllium* (8th ed.) **26**, 82-91 (1930); Ehrlich in *Handbook of Preparative Inorganic Chemistry*, **vol. 1**, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 893. *Review:* Lillie, *USAEC* UCRL 6457, 23 pp (1961).

Light, amorphous powder. mp 2530°. Very sparingly sol in water; slowly sol in concd acids or solns of fixed alkali hydroxides. After ignition it is almost insol in these solvents. Pure (100%) BeO insulates electrically like a ceramic, but conducts heat like a metal. Electrical resistivity in ohm-cm: $>10^{16}$. Dielectric const at 8.5 gigacycles: 6.57.

USE: Manuf of beryllium oxide ceramics, glass; in nuclear reactor fuels and moderators; catalyst for organic reactions.

1217. Beryllium Perchlorate. $BeCl_2O_8$; mol wt 207.91. Be 4.33%, Cl 34.10%, O 61.56%. $Be(ClO_4)_2$. Prepn: *Gmelin's, Beryllium* (8th ed.) **26**, 121 (1930).

Tetrahydrate, very hygroscopic crystals. Holds its water of crystn tenaciously. Soly in water: 148.6 g/100 ml.

1218. Beryllium Potassium Fluoride. *Potassium tetrafluoroberyllate.* BeF_4K_2; mol wt 163.20. Be 5.52%, F 46.56%, K 47.91%. K_2BeF_4. Prepn: *Gmelin's, Beryllium* (8th ed.) **26**, 172 (1930). Review of prepn and properties of beryllium halides: Bell, *Advan. Inorg. Chem. Radiochem.* **14**, 255-332 (1972).

Hard masses. Sol in water, practically insol in alc.

1219. Beryllium Potassium Sulfate. $BeK_2O_8S_2$; mol wt 279.34. Be 3.23%, K 27.99%, O 45.82%, S 22.96%. $BeSO_4 \cdot K_2SO_4$. Prepn: *Gmelin's, Beryllium* (8th ed) **26**, 174 (1930).

Dihydrate, brilliant crystals. Sol in water, concd K_2SO_4 solns; practically insol in alc.

USE: In chromium- and silver-plating.

1220. Beryllium Selenate. BeO_4Se; mol wt 151.97. Be 5.93%, O 42.11%, Se 51.96%. $BeSeO_4$. Prepn: *Gmelin's, Beryllium* (8th ed.) **26**, 144 (1930).

Tetrahydrate, orthorhombic crystals, d 2.03. Changes to the dihydrate at 100° and becomes anhydr at 300°. Freely sol in water; aq solns of beryllium selenate are good solvents for beryllium oxide.

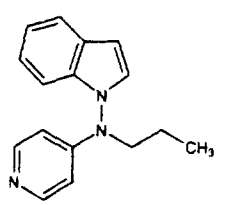
1221. Beryllium Sodium Fluoride. *Sodium tetrafluoroberyllate.* BeF_4Na_2; mol wt 130.99. Be 6.88%, F 58.02%, Na 35.10%. Na_2BeF_4. Prepn: *Gmelin's, Beryllium* (8th ed.) **26**, 169 (1930). Review of prepn and properties of beryllium halides: Bell, *Advan. Inorg. Chem. Radiochem.* **14**, 255-332 (1972).

Orthorhombic or monoclinic crystals. mp ~350°. Sol in water.

1222. Beryllium Sulfate. BeO_4S; mol wt 105.08. Be 8.58%, O 60.91%, S 30.52%. $BeSO_4$. Prepn: *Gmelin's, Beryllium* (8th ed.) **26**, 130-141 (1930). Toxicity study: White *et al., J. Pharmacol. Exp. Ther.* **102**, 88 (1951).

Tetrahydrate, crystals. d 1.71. At about 100° loses $2H_2O$. Very sol in water. Practically insol in alc. LD_{50} i.v. in mice: 0.5 mg Be/kg (White).

1223. Besipirdine. *N-Propyl-N-4-pyridinyl-1H-indol-1-amine;* 1-(propyl-4-pyridylamino)indole. $C_{16}H_{17}N_3$; mol wt 251.33. C 76.46%, H 6.82%, N 16.72%. Cholinomimetic agent with noradrenergic activity. Prepn: R. C. Effland, J. T. Klein, Eur. pat. Appl. **287,982** (1988 to Hoechst); *idem et al.*, U.S. pat. **4,970,218** (1990 to Hoechst-Roussel); of hydrochloride: S. Kongsamut *et al.*, U.S. pat. **5,356,910** (1994 to Hoechst-Roussel). HPLC determn in plasma: R. S. Hsu *et al., J. Chromatog.* **572**, 352 (1991). Mechanism of action study: C. P. Smith *et al., Drug Dev. Res.* **32**, 13 (1994). Pharmacokinetics: J. W. Hubbard *et al., J. Clin. Pharmacol.* **35**, 688 (1995).

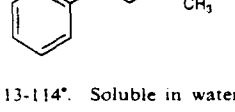


Hydrochloride, $C_{16}H_{17}N_3 \cdot HCl$. *HP-749.* Crystals from methanol, mp 212-214°.

Maleate, $C_{16}H_{17}N_3 \cdot C_4H_4O_4$, crystals from methanol/ether, mp 115-116°.

THERAP CAT: Nootropic.

1224. Betahistine. *N-Methyl-2-pyridineethanamine; 2-[2-(methylamino)ethyl]pyridine;* [2-(2-pyridyl)ethyl]methylamine. $C_8H_{12}N_2$; mol wt 136.20. C 70.55%, H 8.88%, N 20.57%. Prepn: Löffler, *Ber.* **37**, 161 (1904); Walter *et al., J. Am. Chem. Soc.* **63**, 2771 (1941).



Liquid. bp_{30} 113-114°. Soluble in water, alcohol, ether, chloroform.

Dihydrochloride. $C_8H_{12}N_2 \cdot 2HCl$. *Betaserc, Serc, Vasomotal.* Crystals from alc, mp 148-149°.

Maleate, $C_8H_{12}N_2 \cdot C_4H_4O_4$. *Suzutolon.*

but it was suggested that benziodarone should not be used in gouty patients with thyroid irregularities.— J. P. Camus *et al., Revue Rhum. Mal. ostéo-articulaires*, 1973, *40*, 148, per *Thérapie*, 1974, *29*, 15.

Jaundice. The Committee on Safety of Drugs had received reports of 11 cases of jaundice occurring in patients being treated with benziodarone (Cardivix).— J. A. Cahal (letter), *Br. med. J.*, 1964, *2*, 882. Scrutiny of individual case histories and clinical data of the 11 cases of jaundice reported above did not confirm that benziodarone was responsible. Two cases had features which suggested there might be a connection and another case proved to be a carcinoma of the head of the pancreas. As the specific cause was in doubt, Cardivix could not be cleared and the manufacturers had withdrawn the drug from the market pending further information.— J. Valentine *et al.*, *Fisons* (letter), *ibid.*, 882.

Precautions. Benziodarone should be given only with caution to patients with iodine sensitivity and to patients taking anticoagulants.

Interactions. For the effects of benziodarone on anticoagulants, see Ethyl Biscoumacetate, p.771, Phenprocoumon, p.774, and Warfarin Sodium, p.778.

Absorption and Fate. Benziodarone is absorbed from the gastro-intestinal tract. It has been reported that maximum concentrations in plasma occur about 6 hours after a dose; benziodarone is concentrated in the liver. Excretion is mainly in the faeces and may be delayed by reabsorption.

Uses. Benziodarone is a vasodilator which has been used in the prophylaxis of angina pectoris and after myocardial infarction.

Benziodarone has also been given to diminish uricaemia in gout.

Cardiac disorders. References to the use of benziodarone in angina pectoris: P. Dailheu-Geoffroy and J. Nataf, *Presse méd.*, 1961, *69*, 971; P. Davies *et al.*, *Br. med. J.*, 1963, *2*, 359; S. Blake and D. Keelan, *J. Irish med. Ass.*, 1964, *54*, 42.

Hyperuricaemia. In 59 patients with gout (without renal calculi and with a blood-urea concentration not exceeding 1 mg per ml) serum-uric acid concentrations were reduced, in all except one, to less than 70 μg per ml after treatment with benziodarone 300 mg daily, though the effects on blood concentrations and clearance of urea were variable. Side-effects included weakness (11 patients), restless legs (2), dizziness (1), and impotence (2).— A. Ryckewaert *et al.*, *Thérapeutique*, 1971, *47*, 371, per *Abstr. Wld Med.*, 1971, *45*, 772.

In 40 patients with hypertension and normal renal function mean initial serum-uric acid concentrations of 62 μg per ml rose rapidly after commencing treatment with diuretics—usually thiazides—reaching a mean of 88 μg per ml; the concentration fell to normal in all but 1 patient within a week of being given benziodarone 100 to 200 mg daily, the mean value after 4.5 months being 53 μg per ml. Most of 11 patients with impaired renal function also received benefit.— G. Lagrue *et al.*, *Presse méd.*, 1971, *79*, 849, per *Abstr. Wld Med.*, 1971, *45*, 750.

Proprietary Names

Ampliacor *(RBS Pharma, Ital.)*; Amplivix *(Labaz, Belg.; Labaz, Fr.; Sigmatau, Ital.; Labaz, Neth.; Labaz, Switz.)*; Becumaron *(Riedel, Arg.)*; Coronal *(Crinos, Ital.)*; Dilacoron *(Sierochimica, Ital.)*; Dilafurane *(Labaz, Spain)*; Plexocardio *(Benvegna, Ital.)*; Uricor *(Ravizza, Ital.)*.

9212-g

Benzyl Nicotinate.

$C_{13}H_{11}NO_2 = 213.2$.

CAS — 94-44-0.

Benzyl nicotinate is a topical vasodilator used, in a concentration of 2.5%, in rubefacient creams and ointments.

Proprietary Preparations

(under Methyl Nicotinate, p.1626)

9213-q

Betahistine Hydrochloride (PT 9). *N*-Methyl-2-(2-pyridyl)ethylamine dihydrochloride.

$C_8H_{12}N_2,2HCl = 209.1$.

CAS — 5638-76-6 (betahistine); 5579-84-0 (hydrochloride).

A white or creamy-white, odourless, hygroscopic, crystalline powder with a bitter taste. M.p. about 152°. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and ether. Store in airtight containers. Protect from light.

Adverse Effects. Nausea, headache, and exacerbation of peptic ulcer have been reported.

Treatment of Adverse Effects. In the case of severe overdosage the stomach should be emptied by aspiration and lavage. If necessary the circulation should be maintained by infusion of suitable electrolyte solutions. The vasodilator effect of betahistine is stated to be inhibited by antihistamines.

Precautions. Betahistine hydrochloride should be given with care to patients with asthma, peptic ulcer or a history of peptic ulcer. It should not be given to patients with phaeochromocytoma. It has been suggested that it should not be given concomitantly with antihistamines.

Absorption and Fate. Betahistine hydrochloride is readily absorbed from the gastro-intestinal tract. It is converted to 2 metabolites and peak concentrations in blood of the 2 metabolites are achieved within 3 to 5 hours. Most of a dose is excreted in the urine, in the form of the metabolites, in about 3 days.

Uses. Betahistine hydrochloride is an analogue of histamine and is claimed to improve the microcirculation. It is used to reduce the frequency of episodes of dizziness in some patients with Ménière's disease. The usual dose is 8 mg thrice daily taken preferably with meals; not more than 48 mg should be taken in any one day. Betahistine has also been used in the treatment of histamine headache.

Bedsores. In a study in 18 elderly patients with decubitus ulcers, 9 treated for about 3 months with betahistine 2 tablets (each 4 mg) 4 times daily received significantly greater benefit than those treated with placebo.— C. Pecora *et al.*, *Clin. Med.*, 1971, *78* (July), 26. Comment that similar results might follow the application of local heat alone or combined with hydrotherapy.— M. R. Sather *et al.*, *Drug Intell. & clin. Pharm.*, 1977, *11*, 162.

Dementia. Studies into the role of betahistine in arteriosclerosis and dementia: J. H. Seipel and J. E. Floam, *J. clin. Pharmac.*, 1975, *15*, 144; J. H. Seipel *et al.*, *ibid.*, 155; J. S. Meyer *et al.*, *ibid.*, 1974, *14*, 280; J. H. Seipel *et al.*, *ibid.*, 1977, *17*, 140.

Headache. Ninety-three of 160 patients, most of whom suffered from headache of varied cause, were improved after treatment with betahistine hydrochloride, 2 to 25 mg daily.— B. T. Horton and H. von Leden, *Proc. Staff Meet. Mayo Clin.*, 1962, *37*, 692. Of 184 patients with histamine headache, 105 obtained relief after treatment with betahistine hydrochloride, 2 to 25 mg daily.— B. T. Horton, *ibid.*, 713.

Ménière's disease. Reports and studies on betahistine hydrochloride in Ménière's disease: J. C. Elia, *J. Am. med. Ass.*, 1966, *196*, 187; D. M. Le Pere, *Clin. Med.*, 1967, *74* (Apr.), 63; A. Burkin, *ibid.*, *74* (Oct.), 41; J. L. Hicks *et al.*, *Archs Otolar.*, 1967, *86*, 610; *Drug & Ther. Bull.*, 1971, *9*, 42; R. A. Bertrand, *Laryngoscope, St Louis*, 1971, *80*, 889; I. J. C. Frew and G. N. Menon, *Postgrad. med. J.*, 1976, *52*, 101; T. J. Wilmot and G. N. Menon, *J. Lar. Otol.*, 1976, *90*, 833; *Drug & Ther. Bull.*, 1981, *19*, 17.

Proprietary Preparations

Serc *(Duphar, UK)*. Betahistine hydrochloride, available as scored tablets of 8 mg. (Also available as Serc in *Austral., Canad., Fr., S.Afr.*)

Other Proprietary Names

Aequamen (mesylate) *(Ger.)*; Betaserc *(Belg., Cyp., Denm., Egypt, Fin., Greece, Neth., Switz.)*; Deanosart, Hainimed, Medan, Meginalisk, Meniace, Menietol, Merision, Menitazine (all mesylate) (all *Jap.*); Meotets *(Jap.)*; Microser *(Ital.)*; Pyritylulon, Remark, Riptonin (all mesylate) (all *Jap.*); Sinmenier *(Spain)*; Suzotolon, Tenyl-D (both mesylate) (both *Jap.*); Vasomotal *(Ger.)*; Urutal *(Jug.)*.

9214-p

Buphenine Hydrochloride. Nylidrin Hydrochloride *(U.S.P.)*; Nyiidrinium Chloride. 1-(4-Hydroxyphenyl)-2-(1-methyl-3-phenylpropylamino)propan-1-ol hydrochloride.

$C_{19}H_{25}NO_2,HCl = 335.9$.

CAS — 447-41-6 (buphenine); 849-55-8 (hydrochloride).

Pharmacopoeias. In *U.S.*

An odourless, white, crystalline powder. **Soluble** 1 in 65 of water and 1 in 40 of alcohol; slightly soluble in chloroform and ether. A 1% solution in water has a pH of 4.5 to 6.5. **Store** in airtight containers.

Adverse Effects. Buphenine hydrochloride may cause nausea and vomiting, trembling, nervousness, weakness, dizziness, and palpitations.

Treatment of Adverse Effects. In severe overdosage the stomach should be emptied by aspiration and lavage. If necessary, the circulation should be maintained with infusions of suitable electrolytes.

Precautions. Buphenine hydrochloride is contraindicated in patients with myocardial infarction, hyperthyroidism, paroxysmal tachycardia, or severe angina pectoris.

Absorption and Fate. Buphenine hydrochloride is readily absorbed from the gastro-intestinal tract; its effect begins in about 10 minutes, reaches a maximum in about 30 minutes, and lasts for about 2 hours.

Investigations in *dogs* indicated that buphenine is excreted in the urine as the free base and its glucuronide.— H. Li and P. Cervoni, *J. pharm. Sci.*, 1976, *65*, 1352.

Uses. Buphenine produces the effects of beta-adrenoceptor stimulation. It is reported to increase peripheral blood flow mainly by direct action on the arteries and arterioles of the skeletal muscles. It has little effect on the vessels of the skin.

Buphenine has been used in the treatment of peripheral vascular disease.

It has also been used in the treatment of Ménière's disease and other disorders of the internal ear.

The usual initial dose of buphenine hydrochloride is 6 mg by mouth thrice daily, which may be increased to 36 or 48 mg daily in divided doses, if necessary. It has also been given by subcutaneous or intramuscular injection.

Deafness. For the use of buphenine hydrochloride in perceptive deafness, see T. J. Wilmot and J. C. Seymour, *Lancet*, 1960, *1*, 1098.

Dementia. A study of buphenine in elderly patients with cognitive, emotional, and physical impairment.— S. E. Goldstein and F. Birnbom, *J. clin. Psychiat.*, 1979, *40*, 520.

Peripheral vascular disease. On the basis of studies by F.S. Caliva *et al.* (*Am. J. med. Sci.*, 1959, *238*, 174), S. Zetterquist (*Acta med. scand.*, 1968, *183*, 487), and H.L. Karpman and R. Okun (*Geriatrics*, 1972, *27*, 101) there is no indication for the use of buphenine in peripheral vascular diseases.— J. D. Coffman, *New Engl. J. Med.*, 1979, *300*, 713.

Premature labour. Studies of buphenine in the prevention of premature labour: O. Castren *et al.*, *Acta obstet. gynec. scand.*, 1975, *54*, 95; K. S. Koh, *Can. med. Ass. J.*, 1976, *114*, 700; R. Richter, *Am. J. Obstet. Gynec.*, 1977, *127*, 482.

Preparations

Nylidrin Hydrochloride Injection (*U.S.P.*). A sterile solution of buphenine hydrochloride in Water for Injections.

and coma may ensue. Fatalities rarely occur except when other drugs, alcohol or aggravating factors are involved. Hypotension and respiratory depressions are not found frequently unless other drugs have been associated.

Treatment: There is no specific antidote. Gastric lavage performed early after ingestion of the drug may be beneficial. Management consists of supportive measures and close supervision and monitoring. Cardiovascular and CNS stimulants may be used, if necessary. Although oxazepam has a relatively long half-life, the use of dialysis is of questionable value.

Dosage: The dosage must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment.

As with other anxiolytic sedatives, short courses of treatment should usually be the rule for the symptomatic relief of disabling anxiety in psychoneurotic patients and the initial course of treatment should not last longer than 1 week without reassessment of the need for a limited extension. Initially, not more than 1 week's supply of the drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short courses of therapy.

The adult dosage is 30 to 120 mg daily, in divided doses, according to severity of symptoms and patient response. Initiate treatment by lower dose and increase gradually.

Elderly and debilitated patients: The recommended dosage is 5 mg once or twice daily, as tolerated. Initiate treatment always by the lowest dose and increase gradually as needed and tolerated.

Supplied: 10 mg: Each light yellow, scored Titradose tablet, imprinted SERAX and 10, contains: oxazepam 10 mg. Nonmedicinal ingredients: D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and polacrilin potassium. Energy: 2.97 kJ (0.71 kcal). Gluten- and tartrazine-free. Bottles of 100 and 500.

15 mg: Each yellow, scored Titradose tablet, imprinted SERAX and 15, contains: oxazepam 15 mg. Nonmedicinal ingredients: D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and polacrilin potassium. Energy: 2.85 kJ (0.68 kcal). Gluten- and tartrazine-free. Bottles of 100 and 500.

30 mg: Each peach, scored Titradose tablet, imprinted SERAX and 30, contains: oxazepam 30 mg. Nonmedicinal ingredients: FD&C Yellow No. 6 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and polacrilin potassium. Energy: 2.64 kJ (0.63 kcal). Gluten- and tartrazine-free. Bottles of 100 and 500.

(Shown in Product Recognition Section)

SERC® Ⓟ

Solvay Pharma

Betahistine HCl

Antivertigo

Pharmacology: Pathologically, the attacks of vertigo associated with Menière's disease are associated with an accumulation of fluid in the membranous labyrinth of the inner ear (endolymphatic hydrops), and an increase in endolymph pressure. It is less helpful against the progressive decrease in hearing acuity. Information on absorption, metabolism and excretion of betahistine is not available. Animal reproductive studies have not shown any adverse effects.

Indications: May be of value in reducing the episodes of vertigo in Ménière's disease. No claim is made for the effectiveness of betahistine in the symptomatic treatment of any form of vertigo other than that associated with Ménière's disease.

Contraindications: Not to be administered to patients with active peptic ulcer or a history of this condition; pheochromocytoma.

Children: Not recommended for use in children.

Precautions: Caution should be exercised if betahistine is administered to patients with bronchial asthma. Betahistine should not be used concurrently with antihistaminic agents.

Pregnancy and *Lactation:* Safe use of betahistine during pregnancy or lactation, or in women of childbearing age has not yet been established.

Adverse Effects: Occasional patients have experienced gastric upset, nausea and headache.

Dosage: Usual adult dosage has been 4 to 8 mg orally 3 times a day. Therapy is adjusted as needed to maintain patient response. Dosage has ranged from 8 to 32 mg per day. Maximum recommended daily dosage is 32 mg.

Supplied: Each round, white tablet, scored on one side and engraved with "unimed" on the other, contains: betahistine HCl 4 mg. Nonmedicinal ingredients: cornstarch, FD&C Red No. 3, lactose, magnesium stearate and purified silica. Gluten- and tartrazine-free. Bottles of 100.

(Shown in Product Recognition Section)

SERENTIL® Ⓟ

Novartis

Mesoridazine Besylate

Antipsychotic

Pharmacology: Pharmacological studies in laboratory animals have established that mesoridazine has a spectrum of pharmacological activity comparable to thioridazine, except that its effects, other than cataleptic which is weaker, are more pronounced.

Following oral administration, mesoridazine is well absorbed with peak blood levels occurring at 4 hours.

Approximately 30 to 40% of a dose is recovered in the urine and 25 to 30% is recovered in the feces, even after i.m. administration.

Indications: The treatment of both the acute and chronic states of schizophrenia: organic brain syndrome and mental retardation associated with psychotic symptoms or where psychomotor disturbances are predominant; treatment of some patients with symptoms of alcohol withdrawal.

Contraindications: Severe CNS depression, comatose states, blood dyscrasias, bone marrow depression, liver damage, hypersensitivity to mesoridazine; cross sensitivity to other phenothiazines may occur. Hypertension or hypotensive heart disease of extreme degree.

Precautions: Occupational Hazards: Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazine cautiously and to increase the dosage gradually.

Attention should be paid to the fact that phenothiazines are capable of potentiating CNS depressants (e.g. anesthetics, analgesics, hypnotics, antihistamines, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. They may also potentiate quinidine's inhibitory effect on cardiac contractility.

Since ocular pigmentary changes have been reported with phenothiazines of the piperidine class the possibility of this side effect cannot be excluded.

Prolongation of the QT interval, flattening and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving phenothiazine tranquilizers, including mesoridazine. These changes appear to be reversible and related to a disturbance in repolarization. Mesoridazine should be given with caution to patients with heart disease.

Leukopenia, granulocytopenia and/or agranulocytosis have been reported following phenothiazine therapy. The possibility of the occurrence of blood dyscrasia cannot, therefore, be ruled out. Therefore, patients should be observed for any signs or symptoms of blood dyscrasia. It is also advisable to perform regular blood counts, particularly during the first 2 or 3 months of therapy and on the appearance of suspicious clinical signs.

Hypotension, which is typically orthostatic, may occur especially in the elderly and in alcoholic patients with either dosage form. Assumption of the head down supine position will ordinarily bring the blood pressure back to normal. On rare occasions, and more so after parenteral administration of the drug, prolonged and severe hypotension may occur, requiring the use of vasopressors. The administration of epinephrine should be avoided in the treatment of phenothiazine induced hypotension in view of the fact that phenothiazines may induce a reverse epinephrine effect and aggravate the hypotension.

Pregnancy and *Lactation:* Safe use of mesoridazine in human pregnancy has not been established. Therefore, it should not be administered to women of childbearing potential, particularly during the first trimester of pregnancy, unless the expected benefit to the patient outweighs the potential risk to the fetus. Mesoridazine may appear in human breast milk.

Adverse Effects: Drowsiness and hypotension are the most prevalent adverse effects encountered. Sedation, hypotension and other autonomic effects tend to occur more frequently early in the treatment or when initial high doses are used.

When these reactions occur they can usually be controlled by a reduction in dosage. In mild cases of hypotension, the head down position may be adequate. In severe cases of hypotension, a pressor agent such as levarterenol bitartrate may be used. Epinephrine should not be administered, since it may result in a further fall of blood pressure.

The following adverse reactions have been reported with phenothiazine derivatives and may occur with mesoridazine:

Behavioral reactions: oversedation; impaired psychomotor function; paradoxical effects, such as agitation, excitement, insomnia, bizarre dreams, aggravation of psychotic symptoms; and toxic confusional states.

CNS: extrapyramidal reactions, including Parkinsonism (with motor retardation, rigidity, masklike facies, tremor, salivation, etc.); dystonic reactions (including facial grimacing, tics, torticollis, oculogyric crises, etc.); and akathisia. Persistent dyskinesias resistant to treatment have also been reported. In addition, slowing of EEG, disturbed body temperature, and lowering of the convulsive threshold have occurred.

Tardive dyskinesia may appear in some patients on long-term antipsychotic therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. All antipsychotic agents should be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. The physician may be able to reduce the risk of this syndrome by minimizing the unnecessary use of neuroleptics and reducing the dose or discontinuing the drug, if possible, when manifestations of this syndrome are recognized, particularly in patients over the age of 50. Fine vermicular movements of the tongue may be an early sign of the syndrome. If the medication is stopped at that time, the syndrome may not develop.

Autonomic nervous system: dry mouth, fainting, stuffy nose, photophobia, blurred vision, miosis.

Gastrointestinal: anorexia, increased appetite, gastric irritation, nausea, vomiting, constipation, paralytic ileus.

Endocrine system: altered libido, menstrual irregularities, lactation, false positive pregnancy tests, inhibition of ejaculation, gynecomastia, weight gain.

Skin: itching, rash, hypertrophic papillae of the tongue, angioneurotic edema, erythema, exfoliative dermatitis, contact dermatitis.

Cardiovascular effects: hypotension, tachycardia, ECG changes (see Precautions).

Blood dyscrasias: agranulocytosis, leukopenia, granulocytopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic reactions: fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: jaundice, biliary stasis.

Urinary disturbances: retention, incontinence.

Abnormal pigmentation: more recently, a peculiar skin-eye syndrome has been recognized as an adverse effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of skin or conjunctiva and/or discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Although retinal pigmentation has not been observed with mesoridazine, patients receiving higher doses of mesoridazine for prolonged periods should have periodic complete eye examinations.

Miscellaneous: Unexpected and sudden deaths have been reported in hospitalized psychotic patients receiving phenothiazines. In some unexpected deaths, myocardial lesions have been observed. Previous brain damage or seizures may also be predisposing factors: high doses should be avoided in known seizure patients. Several patients have shown sudden exacerbations of psychotic behavior patterns shortly before death. Autopsy findings have also revealed acute fulminating pneumonia or pneumonitis and aspiration of gastric contents. The physician should therefore be alerted to the possible development of "silent pneumonias".

Database: Medline <1966 to present>

<1>
Unique Identifier
95227410
Authors
Tighilet B. Leonard J. Lacour M.
Title
Betahistine dihydrochloride treatment facilitates vestibular compensation in the cat.
Source
Journal of Vestibular Research. 5(1):53-66, 1995 Jan-Feb.
Abstract
Unilateral lesion of the vestibular system induces posturo-locomotor deficits that are compensated for with time. Drug therapy is currently used to improve the recovery process and to facilitate vestibular compensation. Betahistine dihydrochloride is an histamine-like substance that has been employed in vestibular pathology; it was found effective in many forms of vertigo and in vestibular-related syndromes. Investigations performed in animal models have shown betahistine-induced neuronal modulations in the vestibular nuclei complex and interactions with the H1 and H3 histamine receptors. Potentially, this substance is therefore capable to interfere with some recovery mechanisms and to improve the behavioral adaptations. But there is at present a total lack of data concerning the influence of betahistine treatment on vestibular compensation in animal models. The aim of this study was to understand the pharmacological activity of betahistine in the restoration of posture and locomotor balance functions in unilateral vestibular neurectomized cats. Posture recovery was assessed by quantifying the surface reaction of the cat's support as measured while standing erect on its four legs, at rest. Locomotor balance recovery was determined using the rotating beam test, by measuring the maximal performance (max. P.) of the cat and its locomotion speed regulation during the postoperative time period. We have compared the recovery profile and time course of these static (posture) and dynamic (equilibrium) functions in three groups of cats. Two experimental groups were treated at daily doses of 50 mg/kg and 100 mg/kg, respectively. Betahistine dihydrochloride was given orally until complete recovery of posturolocomotor functions. One untreated control group served as the reference. Results showed that postoperative treatment strongly accelerated the recovery process in both

treated groups, inducing a time benefit of around 2 weeks as compared to the controls. Maximum performance of the cats on the rotating beam as well as locomotion speed regulation were highly correlated to the postoperative development of the cat's support surface, indicating that compensation of the static vestibulospinal deficits conditioned the subsequent locomotor balance recovery. These behavioral data showed that betahistine dihydrochloride constitutes a useful drug therapy for the symptomatic treatment of central vestibular disorders in our animal model of unilateral vestibular lesion. Improvement of vestibular compensation under betahistine postoperative treatment, as evidenced here for the posture and locomotor balance functions, is discussed both in terms of aspecific effect (histamine-induced increase of the level of vigilance) or more direct action in the vestibular nuclei (histamine-induced rebalance of neuronal activity on both sides).

<2>
Unique Identifier
84113189
Authors
Oosterveld WJ.
Title
Betahistine dihydrochloride in the treatment of vertigo of peripheral vestibular origin. A double-blind placebo-controlled study.
Source
Journal of Laryngology & Otology. 98(1):37-41, 1984 Jan.
Abstract
A double-blind, cross-over, placebo-controlled study of betahistine dihydrochloride (12 mg, t.i.d.) was carried out in patients with vertigo of peripheral vestibular origin. Twenty-four patients completed the study, which consisted of two six-week treatment periods. The patients were diagnosed as suffering from Meniere's disease (15 patients), vertigo due to other (specified) causes (five patients), or vertigo of unknown origin (four patients). Patients were examined by the investigator at the start of the study and were re-assessed at three-weekly intervals. In addition, they recorded the nature, frequency and severity of their symptoms on diary cards. Both the incidence and severity of dizziness (the predominant presenting complaint) were found to be significantly reduced during betahistine treatment ($p = 0.004$). The occurrence of nausea and vomiting was also significantly reduced during betahistine treatment ($p = 0.014$ and 0.036

respectively). There were no statistically significant differences in the results of audiometric or vestibulometric tests, or in the severity of tinnitus or deafness, between the two treatment periods. The overall comparisons of the two periods made by both the patients and the investigator were significantly in favour of betahistine (p less than 0.001). All diagnostic groups responded favourably to betahistine, confirming the efficacy of betahistine in the symptomatic treatment of peripheral vestibular vertigo. No unwanted signs or symptoms were reported.

<3>
Unique Identifier
82165791
Authors
Petermann W. Mulch G.
Title
[Long-term therapy of Meniere's disease. Comparison of the effects of betahistine dihydrochloride and hydrochlorothiazide]. [German]
Source
Fortschritte der Medizin. 100(10):431-5, 1982 Mar 11.
Abstract
During the last few years betahistine-dihydrochloride has been used extensively in the conservative treatment of M. Meniere. The question has arisen as to whether betahistine-dihydrochloride is more effective than diuretics. The effect of betahistine-dihydrochloride was compared to that of hydrochlorothiazide on 32 M. Meniere-patients. The patients were initially kept under observation for 3 months without medication apart from symptomatic anti-vertigo agents. The patients were then assigned to 2 groups each of 16 subjects and received either 3 X 8 mg betahistine-dihydrochloride or 3 X 25 mg hydrochlorothiazide for 6 months under double-blind conditions. Before and during treatment subjective symptoms such as vertigo, attacks of dizziness, tinnitus, sensation of blockage in the ear and general well-being were assessed at 4-weekly intervals. Apart from this the objective symptoms as measured by pure tone audiograms, Frenzel-test and electronystagmography were recorded. At the moment betahistine-dihydrochloride seems to be the drug of choice for Meniere-patients with a fluctuating auditory threshold. During the 6 months treatment period an impressive reduction in the frequency, severity and duration of the attacks of vertigo as well as an improvement in the general condition was found in all patients. In contrast the

diuretic hydrochlorothiazide seemed to show a distinct therapeutic effect on vertigo and general well-being principally during the first few months of treatment in patients with a constant auditory threshold.

<4>
Unique Identifier
92108928
Authors
Fraysse B. Bebear JP. Dubreuil C. Berges C. Dauman R.
Title
Betahistine dihydrochloride versus flunarizine. A double-blind study on recurrent vertigo with or without cochlear syndrome typical of Meniere's disease.
Source
Acta Oto-Laryngologica - Supplement. 490:1-10, 1991.
Abstract
This study was designed to compare the efficacy and safety of betahistine dihydrochloride and flunarizine. All patients included in this multicenter, double-blind, randomized trial showed a specific pattern of vertigo, i.e. recurrent paroxysmal vertigo with or without the cochlear symptoms typical of Meniere's disease. Fifty-five patients were treated for 2 months (28 in the betahistine group and 27 in the flunarizine group). Analysis of intra-group symptom changes demonstrated a greater efficacy for betahistine. Statistically significant decreases in duration and severity of attacks, and in the presence of vegetative symptoms were seen in the betahistine group after the first and second months of treatment, whereas in the flunarizine group this was the case only at the end of the first month of treatment. Furthermore in the betahistine group, statistically significant decreases occurred for the other major criteria, including number of attacks, evidence of vestibular dysfunction, and presence of cochlear symptoms. Adverse effects were similar to those reported in previous studies of both products: stomach pains only with betahistine, and drowsiness, asthenia, and depression with flunarizine.

<5>
Unique Identifier
90125179
Authors
Cullen JR. Hall SJ. Allen RH.
Title
Effect of betahistine dihydrochloride compared with

cinnarizine on induced vestibular nystagmus.
Source
Clinical Otolaryngology. 14(6):485-7, 1989 Dec.
Abstract
The effect of betahistine compared with cinnarizine on induced vestibular nystagmus was evaluated using a rotating chair, in 6 healthy volunteers. The subjects underwent a slow acceleration followed by a sudden stop. Electronystagmograph tracings were taken initially as pretreatment control values, and after betahistine 8 mg t.i.d. and cinnarizine 15 mg t.i.d. had been taken. The duration of nystagmus and average eye speed were measured. No difference was recorded in either parameter between the pretreatment rotation and that following betahistine (P greater than 0.05). A significant difference (P less than 0.05) was seen in the duration of nystagmus during initial acceleration, and in average eye speed following the sudden stop after treatment with cinnarizine.

<6>
Unique Identifier
89269630
Authors
Pfaltz CR. Aoyagi M.
Title
Calcium-entry blockers in the treatment of vestibular disorders.
Source
Acta Oto-Laryngologica - Supplement. 460:135-42, 1988.
Abstract
Based upon the results of a double-blind study carried out in a series of 120 patients suffering from vertigo and objective vestibular symptoms, we made the following observations during the treatment of vestibular disorders by means of calcium-entry blockers: Subjective symptoms regress fairly well during treatment, but no better than after betahistine-dihydrochloride (BHC) or thietylperazine therapy (TP). Objective assessment of the therapeutic action of calcium antagonists on vestibular dysfunction is based on the results of the Harmonic Acceleration test, which was carried out by using a computerized rotatory chair. The most reliable parameter with respect to the objective assessment of the experimentally induced vestibular responses (VOR) is the gain. Our test results show a progressive decrease in GAIN, indicating a depressive or inhibitory effect of the calcium antagonist flunarizine upon the VOR. If we compare these results with those obtained in the betahistidine- and thiethylperazine

groups, we cannot confirm the same decline in GAIN within the latter two groups. A statistical analysis demonstrates a significant difference between the F-gain on the one hand, and the BHC gain and TP gain on the other hand.

<7>
Unique Identifier
87216546
Authors
Oosterveld WJ.
Title
Effect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study.
Source
Clinical Otolaryngology. 12(2):131-5, 1987 Apr.
Abstract
The effect of betahistine on vestibular nystagmus induced by means of a torsion swing was tested in 10 subjects. Each individual received, in a randomized double-blind study, 3 different single oral dosages of betahistine (8, 16 and 32 mg) on 3 different occasions. Electronystagmographic tracings were taken at different time-intervals after drug intake. At 3-4 hours after a dose of 8 mg betahistine the nystagmus duration was reduced by 35%, after 16 mg betahistine by 48% and after 32 mg betahistine by 59% (mean values). All these differences in dose-response are highly significant (P less than 0.0005). It can be concluded from these results, that a dose of 3 X 8 mg or 3 X 16 mg betahistine daily will be efficacious in maintenance treatment of vertigo, and a dose of 3 X 24 mg betahistine daily will have even more effect.

<8>
Unique Identifier
87052919
Authors
Deering RB. Prescott P. Simmons RL. Downey LJ.
Title
A double-blind crossover study comparing betahistine and cinnarizine in the treatment of recurrent vertigo in patients in general practice.
Source
Current Medical Research & Opinion. 10(4):209-14, 1986.
Abstract
A double-blind crossover study was carried out in general practice in 88 patients with peripheral vertigo of unknown origin to compare the efficacy and tolerance of 12 mg

betahistine dihydrochloride and 15 mg cinnarizine. Patients were allocated at random to receive 2 tablets 3-times daily of one or other drug for 3 consecutive months before being crossed over to the alternative medication for a further 3 months. Severity of symptoms was assessed at 4-week intervals using the Clinical Global Impression scale and patients kept a record in a daily diary of the frequency and duration of attacks. Details were also recorded of any side-effects reported. The results were analyzed for 46 patients who completed the 6-month study period. Both drugs were shown to be equally effective in reducing the duration and severity of symptoms. Significantly fewer attacks of vertigo, however, occurred during betahistine therapy. Side-effects were the most common reason for dropping out whilst on cinnarizine (9 patients) and were complained of by 38 patients during the study (16 only when on betahistine, 19 only on cinnarizine, 3 whilst on both drugs). The most frequently reported were drowsiness or lethargy affecting 16 patients on cinnarizine and 7 on betahistine.

Clin. Otolaryngol. 1987, **12**, 131–135

Effect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study

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OOSTERVELD W. J. (1987) *Clin. Otolaryngol.* **12**, 131–135

Effect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study

The effect of betahistine on vestibular nystagmus induced by means of a torsion swing was tested in 10 subjects. Each individual received, in a randomized double-blind study, 3 different single oral dosages of betahistine (8, 16 and 32 mg) on 3 different occasions. Electronystagmographic tracings were taken at different time-intervals after drug intake. At 3–4 hours after a dose of 8 mg betahistine the nystagmus duration was reduced by 35%, after 16 mg betahistine by 48% and after 32 mg betahistine by 59% (mean values). All these differences in dose-response are highly significant ($P < 0.0005$). It can be concluded from these results, that a dose of 3×8 mg or 3×16 mg betahistine daily will be efficacious in maintenance treatment of vertigo, and a dose of 3×24 mg betahistine daily will have even more effect.

Keywords *betahistine vertigo treatment vestibular function*

In several double blind placebo controlled clinical studies[1–5] betahistine has been proved to be effective in the treatment of patients suffering from episodes of peripheral vertigo, such as are present in Ménière's disease. The doses used in these studies ranged from 24 to 48 mg betahistine daily. Clinical observations suggested that a dose of 72 mg (3×24 mg) betahistine daily might be even more effective in the treatment of these patients. The aim of the present study was to find objective support for this impression.

Methods

VOLUNTEERS

Ten normal subjects, 6 males and 4 females between 23 and 30 years of age, volunteered to participate in the study. They all had a history free from neurological and cochleovestibular pathology. All of them received 3 different single oral doses of betahistine on 3 different occasions with an inter-test interval of 1 week. The sequence of the dose strength was randomized. Betahistine (8, 16 and 32 mg) was supplied in individually coded opaque capsules of identical appearance.

VESTIBULAR NYSTAGMUS

Vestibular nystagmus was induced by means of a torsion swing, the oscillations provoking alternating angular accelerations in the swing and in the subject sitting on it. These accelerations stimulate the horizontal semicircular canals of the vestibular organ, resulting in nystagmus in the horizontal plane. This nystagmus can

* Trade marks: Serc®, Betaserc®, Vasomotal®.

be recorded electronystagmographically. Each time the torsion swing test is repeated in a subject, the provoked nystagmus will be the same, if the initial amplitude of the swing movement is kept constant.

If a drug known to reduce vestibular reflexes has been administered, the parameters characteristic for the nystagmus will change. The most relevant ENG parameters are the duration of nystagmus, the speed of the slow component and the frequency. The duration of the slow nystagmus phase was used in the present study.

During the study, the oscillation time of the swing was 16 seconds; this time remained constant at each test point and the average duration of nystagmus for each individual was calculated from 20 measurements at each test point. The average duration in the torsion swing test performed before drug administration was taken as 100% in each individual subject.

The duration of nystagmus, following drug administration, was calculated as a percentage of the pre-treatment duration. The duration of nystagmus was measured before administration of the drug and at ½, 1, 2, 3, 4, 6 and 8 h after. This method has also been used in previous experiments with other drugs.[6-8]

STATISTICS

The following statistical tests were used: Wilcoxon matched-pair signed-rank test, and Pearson's correlation coefficient. A two-tailed *P*-value of less than 0.05 was regarded as being statistically significant.

Results

Ten volunteers received a single oral dose of betahistine (8, 16 or 32 mg) in a randomized and double-blind fashion, on 3 different occasions with an inter-test interval of 1 week. The absolute values of the duration of nystagmus at the onset of each investigation are listed in Table 1.

It is clear that the 3 values before administration of the drug for each subject are very similar, the standard error of the mean (SEM) is less than 0.7% for all subjects. Table 1 revealed no significant differences in the absolute values of the nystagmus duration at the onset of the investigation.

TIME-INTENSITY

The mean courses of the duration of nystagmus with respect to time, induced by the 3 different dosages of betahistine in the 10 volunteers, are plotted in Figure 1. This shows that betahistine significantly reduces the duration of nystagmus when given in doses of 8 mg, 16 mg and 32 mg ($P < 0.0005$) and that the higher the dose the more marked is the reduction in the duration of the nystagmus (again $P < 0.0005$).

DOSE-RESPONSE

For each volunteer the lowest values of the duration of nystagmus at the 3 different doses were listed and also the time (t_{max}) after administration of the drug at which these lowest values occurred. By subtracting the lowest value from the baseline value (= 100%) the maximal reduction of the nystagmus duration, induced by the 3 different doses in the 10 subjects, could be determined (see Table 2).

The results showed that 16 mg betahistine was more effective ($P < 0.0005$) in reducing the nystagmus duration (mean reduction 48%) than 8 mg betahistine (mean reduction 35%). Further, 32 mg betahistine was more effective ($P < 0.0005$) (mean reduction 59%) than 16 mg betahistine.

The time-interval between drug intake and the maximal effect (t_{max}) was significantly shorter ($P < 0.005$) after a dosage of 8 mg betahistine than after 16 or 32 mg betahistine. The t_{max} between the dosage of 16 and 32 mg betahistine (Table 2) was not significantly different.

The reduction of the duration of

Table 1. Nystagmus duration on torsion swing test before betahistine (blank values)

	Duration of nystagmus (s)				
Test subject	*8 mg*	*16 mg*	*32 mg*	*Mean*	*SEM*
1	9.51	9.59	9.61	9.57	0.03
2	9.45	9.47	9.43	9.45	0.01
3	10.11	9.98	10.21	10.10	0.07
4	9.63	9.61	9.57	9.60	0.02
5	9.67	9.62	9.63	9.64	0.02
6	9.58	9.63	9.56	9.59	0.02
7	10.05	9.95	10.03	10.01	0.03
8	9.38	9.43	9.39	9.40	0.02
9	9.84	9.81	9.78	9.81	0.02
10	10.39	10.37	10.41	10.39	0.01
Mean	9.76	9.75	9.76	—	—
s.d.	0.34	0.29	0.33	—	—
SEM	0.11	0.09	0.10	—	—

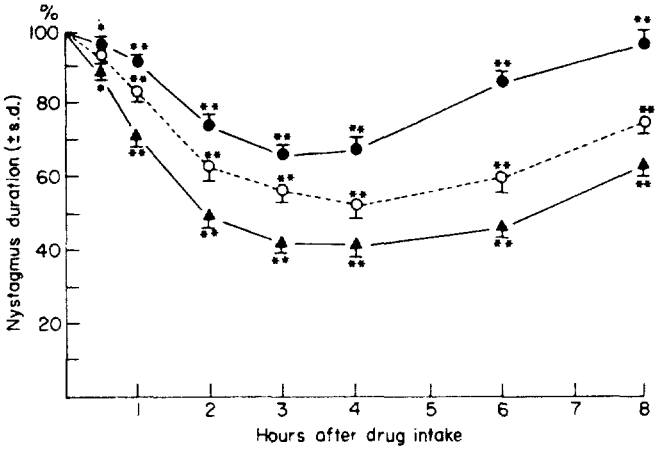

Figure 1. Reduction of nystagmus duration caused by 3 different single oral dosages of betahistine with respect to time in 10 volunteers (mean values ± s.d.). $n = 10$, * = $P < 0.05$; ** = $P < 0.0005$, ●——● = 8 mg; ○ - - - - ○ = 16 mg; ▲——▲ = 32 mg.

Table 2. The maximal reduction of the duration of nystagmus and the time this maximal effect occurred after drug intake

	8 mg betahistine		*16 mg betahistine*		*32 mg betahistine*	
Subject	t_{max} *(h)*	*reduction (%)*	t_{max} *(h)*	*reduction (%)*	t_{max} *(h)*	*reduction (%)*
1	3	38	4	47	4	55
2	4	41	4	53	4	57
3	3	41	3–4	46	4	61
4	3	31	4	44	4	63
5	3	33	4	50	3	62
6	3	34	4	45	4	59
7	3	32	4	50	4	58
8	3	37	4	51	4	62
9	3	34	4	46	4	58
10	3–4	31	4	48	3	56
Mean	3.2	35*	4.0†	48	3.8†	59*
s.d.	0.3	3.8	0.2	2.9	0.4	2.8
SEM	0.1	1.2	0.05	0.9	0.1	0.9

* Wilcoxon $P < 0.0005$, compared with reducing properties of 16 mg betahistine.
† Wilcoxon $P < 0.005$, compared with t_{max} after 8 mg betahistine.

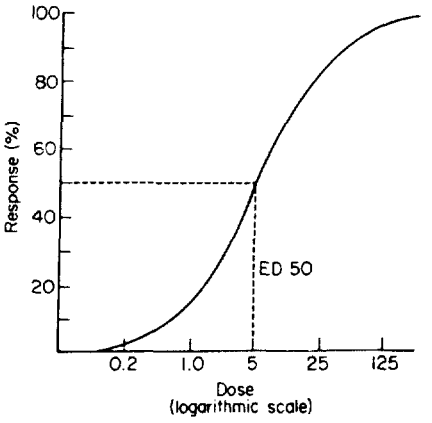

Figure 2. A log dose-response (LDR) curve. The horizontal axis shows the dose on a logarithmic scale. The curve shows the relationship between the dose and the percentage of the maximal response induced by this dose.

nystagmus was plotted in a log dose-response curve. A log dose-response (LDR) curve is an S-shaped curve with a linear part in the middle (see Figure 2). The ED_{50} is the dose which causes 50% of the maximal effect.

Semi-logarithmic curve fitting of all 30 test-values (see Table 2), revealed a high correlation ($r = 0.95$) between these test-values. Therefore these test-values must be on the linear part of the LDR curve and the maximal effect on reduction of nystagmus duration induced by a single dose of betahistine must be reached at a dosage over 32 mg ($P < 0.0005$). These results are shown in Figure 3.

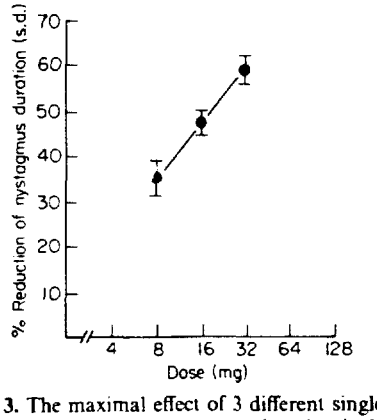

Figure 3. The maximal effect of 3 different single oral doses of betahistine on nystagmus duration in 10 volunteers: a part of the log dose-response curve. $n = 10$; $y = a + b \ln x$: ($a = -0.37$, $b = 17.2$); $r = 0.95$; $P < 0.005$.

Discussion

Vestibular nystagmus induced by means of a torsion swing, proved to be an excellent objective method of studying the effect of different doses of betahistine on the duration of nystagmus in humans. The present study has demonstrated that betahistine is undoubtedly potent in reducing this duration (up to 63% reduction in this study). All 3 doses of betahistine had a clear effect on the duration of nystagmus, but the single dose of 32 mg betahistine proved to be more effective than 16 mg betahistine, the latter dose being in turn more effective than 8 mg betahistine. The nystagmus duration reducing properties of the 3 dosages lie on the linear part of the log dose-response curve (see Figure 3), therefore the maximal effect of betahistine on nystagmus duration can be expected to occur following a single dose of over 32 mg and this maximal effect occurred 3–4 h after drug intake. The volunteers reported no side-effects. From these results it can be concluded that 3×8 mg or 3×16 mg betahistine daily will be efficacious in the maintenance treatment of vertigo, but that a dosage of 3×24 mg betahistine daily will have even more effect. It is unlikely that the maximal effect of betahistine on vertigo is reached at a dosage of 3×24 mg daily.

A comparison with the results from previous experiments[6-8] indicates that the effect of 8 mg betahistine on reduction of nystagmus duration is similar to that of the antihistamines meclozine, chlorcyclizine, cinnarizine (15 and 45 mg) and flunarizine (10 and 30 mg). Betahistine, however, has no sedating properties. The effects of 16 and 32 mg betahistine are more pronounced than those of the antihistamines.

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A double-blind placebo-controlled study

by

W. J. OOSTERVELD (Amsterdam, The Netherlands)

Introduction

Betahistine dihydrochloride (Serc[R])* is an histamine analogue which has been shown, in several placebo-controlled double-blind studies, to be safe and effective in relieving the symptoms of patients suffering from Menière's disease (Hicks *et al.*, 1967; Wolfson *et al.*, 1967; Frew and Menon, 1976; Wilmot and Menon, 1976). The efficacy of betahistine in this condition is believed to be due to its proven ability to improve the microcirculation of the inner ear (Kubicek and Anderson, 1967; Martinez, 1972).

The present study was designed to examine the efficacy of betahistine in patients with different types of peripheral vestibular vertigo. A recently reported, placebo-controlled study of betahistine in patients with vertigo of peripheral origin without established cause, provides preliminary evidence of the efficacy of betahistine in these patients (Canty *et al.*, 1981).

The study was carried out between March 1978 and May 1981 in the Ear, Nose and Throat Department of the Wilhelmina Gasthuis, Amsterdam, The Netherlands.

Materials and Methods

Patient population

Male or female patients under 70 years of age, who had been suffering from peripheral vertigo (according to the criteria of Kane and Strong, 1957) for at least two months were eligible for the study. Patients were excluded from the study if their vertigo was considered to be due to infections of the middle-ear or sinuses, to be of ocular, central or psychic origin; or to be caused by cervical spondylosis or internal disorders. Also excluded were patients suffering from bronchial asthma or peptic ulcer, because of histaminergic properties of betahistine. Informed consent was received from all patients prior to entry into the study.

Study design

The study was carried out according to a double-blind, cross-over design. There were two six-week treatment periods. One group of patients received one tablet of 12 mg betahistine three times daily during the first treatment period and matching placebo tablets three times daily during the second, while the other group received the two treatments in the reverse order.

Observations and measurements

Prior to entry into the study all patients received a thorough clinical examination, including disease history and laboratory tests, and underwent a battery of vestibulo-

* Serc[R] is a registered trademark of Duphar B.V., Amsterdam, The Netherlands.

metric tests (using electronystagmography) and audiometry. Patients were then allocated to one of three diagnostic categories: Menière's disease, other specified types of peripheral vertigo, or peripheral vertigo of unknown origin. The diagnosis of Menière's disease was reserved for patients with a combination of paroxysmal vertigo, tinnitus and varying hearing loss, with demonstrable recruitment on audiometric testing.

During the study period patients were given diary cards on which they were asked to record each day the nature, frequency and severity of their vertiginous complaints. At the end of each six-week treatment period the patients returned to the out-patient clinic and were questioned by the investigator on the overall status of their complaints during the previous six weeks. The following items were rated at these visits using a numerical scoring system:

Item	*Rating*
1. Interference of vertigo with daily activities	Minimally or incidentally hampered/at times unable to work or carry out more difficult activities/seriously limited in work or activities.
2. Severity of deafness 3. Severity of tinnitus	Mild/moderate/severe.
4. Character of deafness 5. Character of tinnitus	Continuous constant/intermittent/continuous fluctuating.

Vestibulometry and audiometry were also repeated at the end of each treatment period; at the end of the study, the investigator compared the results of the tests performed at the end of week six with those from week 12.

At the end of the study both the investigator and the patient were asked to compare the overall condition of the patient's vertigo during the two treatment periods by choosing one of the following statements:

—no difference between periods.
—last period slightly better.
—last period much better.
—first period slightly better.
—first period much better.

Results

Twenty-seven patients entered the study, three of whom failed to complete the full 12 weeks (see Table I). The results in these three patients have been excluded from the statistical analysis of efficacy. Of the remaining 24 patients, 11 received placebo treatment first and 13 received betahistine first. The pre-treatment comparability of the two groups was good, both with respect to demographic data and the results of the various pre-treatment assessments (Table II).

Data on the efficacy of the two treatments were derived from two sources; the patient diary cards, and the assessments at the end of each treatment period. Adequately completed diary cards are available for 15 of the 24 patients included in the analysis. The data on these cards (Table III) reveal that statistically, both the incidence and severity of dizziness were significantly lower during betahistine treatment than during placebo ($p = 0.004$). The occurrence of nausea and vomiting was also significantly reduced during betahistine treatment ($p = 0.014$ and 0.036 respectively).

These results are supported by the results of the investigator's assessment of the patients' status at the end of the two study periods. The investigator judged that vertigo had interfered less with the patients' activities of daily life during the betahistine treatment period than during the placebo period ($p = 0.035$, Table IV).

The severity of tinnitus decreased in three patients during the betahistine treatment period and in one patient during the placebo

TABLE I

PATIENTS FAILING TO COMPLETE THE STUDY

Patient no.	Time of leaving study	Treatment	Reason
2751	After week six	Placebo	Unknown
2752	Week one	Placebo	Refused co-operation
2753	Week one	Betahistine	Took other antivertiginous medication

period. The severity of deafness decreased in one patient during the placebo period.

Consideration of the objective data (from vestibulometry and audiometry) revealed no significant differences between the two treatments.

Statistically, the overall comparisons of the patient's vertigo during the two treatments made by both the patients and the investigator (Table V) were significantly in favour of betahistine ($p = 0.001$). While all groups of patients responded favourably to betahistine treatment, the response of the non-Menière patients was, in the investigator's opinion, more impressive than that of the patients with a diagnosis of Menière's disease ($p = 0.06$).

No unwanted signs or symptoms were reported by the patients or observed by the investigator.

TABLE II

PRE-TREATMENT COMPARABILITY OF TREATMENT GROUPS

Variable	Placebo-Betahistine group	Betahistine-Placebo group
Number (excluding drop-outs)	12(11)	15(13)
Sex: Male	7	7
Female	5	8
Diagnosis: Menière's disease	6	12
Other:		
Menière's syndrome*	2	—
Paroxysmal vertigo	1	—
Dead labyrinth (r)	—	1
Chronic dizziness	—	1
Unknown	3	1
Electronystagmography:		
Spontaneous nystagmus	7	12
Position-induced	7	11
Audiometry:		
Pure-tone: abnormal	10	14
Speech: with recruitment	6	12

* Not fulfilling all criteria for Menière's disease: see Materials and Methods.

Discussion

The results of the present study confirm the finding of Canty *et al.* (1981) that the effectiveness of betahistine in treating vertigo of peripheral vestibular origin is not restricted to patients with a diagnosis of Menière's disease.

Audiometric and vestibulometric measurements were made, principally to confirm diagnosis, and no significant improvements and/or differences between treatment periods were expected or observed.

The main presenting symptom for all patients in the study was dizziness. There was statistically a highly significant reduction in both the incidence and severity of dizziness during betahistine treatment and this improvement was accompanied by a reduction in the incidence of nausea and vomiting.

Statistically, the overall comparisons made between the two treatments were also highly significantly in favour of betahistine. The positive response of the patients not diagnosed as suffering from Menière's disease confirms the efficacy of betahistine in the symptomatic treatment of other types of peripheral vestibular vertigo.

These results show betahistine treatment to be useful in treating dizziness of unspecified peripheral vestibular origin. It is possible that an even more impressive response would be achieved with a higher daily dose of betahistine (author's opinion).

Summary

A double-blind, cross-over, placebo-controlled study of betahistine dihydro-

TABLE III

DATA FROM THE PATIENT DIARY CARDS (15 PATIENTS)

Variable	Placebo period	Betahistine period	p
Number days with dizziness	9.1	5.9	0.004
Total dizziness severity score*	19.1	10.7	0.004
Total duration of dizziness (h)†	12.8	7.8	0.012
Number days with nausea	5.2	3.7	0.014
Number days with vomiting	3.5	1.9	0.036

* Severity scored as mild (1), moderate (2) or severe (3).
† n = 13.

TABLE IV

INTERFERENCE OF VERTIGO WITH ACTIVITIES OF DAILY LIFE (RATED BY THE INVESTIGATOR AT THE END OF EACH TREATMENT PERIOD AND COMPARED RETROSPECTIVELY)

Diagnosis	Menière's disease	Other/unknown	Total
Less on betahistine treatment	7	5	12
Less on placebo treatment	2	1	3
No difference	6	3	9
p-value	0.18	0.22	0.035

TABLE V

OVERALL COMPARISON OF TREATMENT PERIODS

	Investigator's opinion			Patient's opinion		
Judgement	Menière's disease	Other/unknown	All	Menière's disease	Other/unknown	All
Betahistine much better	4	5	9	6	6	12
Betahistine slightly better	6	4	10	4	3	7
No difference	1	—	1	1	—	1
Placebo slightly better	4	—	4	3	—	3
Placebo much better	—	—	—	1	—	1
p-value	0.048	0.006	0.001	0.059	0.006	0.001

p-value Menière's disease *vs.* other/unknown (Investigator's opinion): 0.06.
p-value Menière's disease *vs.* other/unknown (Patient's opinion): 0.10.

chloride (12 mg., t.i.d.) was carried out in patients with vertigo of peripheral vestibular origin. Twenty-four patients completed the study, which consisted of two six-week treatment periods. The patients were diagnosed as suffering from Menière's disease (15 patients), vertigo due to other (specified) causes (five patients), or vertigo of unknown origin (four patients). Patients were examined by the investigator at the start of the study and were re-assessed at three-weekly intervals. In addition, they recorded the nature, frequency and severity of their symptoms on diary cards. Both the incidence and severity of dizziness (the predominant presenting complaint) were found to be significantly reduced during betahistine treatment ($p = 0.004$).

The occurrence of nausea and vomiting was also significantly reduced during betahistine treatment ($p = 0.014$ and 0.036 respectively). There were no statistically significant differences in the results of audiometric or vestibulometric tests, or in the severity of tinnitus or deafness, between the two treatment periods. The overall comparisons of the two periods made by both the patients and the investigator were significantly in favour of betahistine ($p<0.001$). All diagnostic groups responded favourably to betahistine, confirming the efficacy of betahistine in the symptomatic treatment of peripheral vestibular vertigo. No unwanted signs or symptoms were reported.

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A double-blind placebo-controlled study

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The present study was designed to examine the efficacy of betahistine in patients with different types of peripheral vestibular vertigo. A recently reported, placebo-controlled study of betahistine in patients with vertigo of peripheral origin without established cause, provides preliminary evidence of the efficacy of betahistine in these patients (Canty *et al.*, 1981).

The study was carried out between March 1978 and May 1981 in the Ear, Nose and Throat Department of the Wilhelmina Gasthuis, Amsterdam, The Netherlands.

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Patient population

Male or female patients under 70 years of age, who had been suffering from peripheral vertigo (according to the criteria of Kane and Strong, 1957) for at least two months were eligible for the study. Patients were excluded from the study if their vertigo was considered to be due to infections of the middle-ear or sinuses, to be of ocular, central or psychic origin; or to be caused by cervical spondylosis or internal disorders. Also excluded were patients suffering from bronchial asthma or peptic ulcer, because of the histaminergic properties of betahistine. Informed consent was received from all patients prior to entry into the study.

Study design

The study was carried out according to a double-blind, cross-over design. There were two six-week treatment periods. One group of patients received one tablet of 12 mg betahistine three times daily during the first treatment period and matching placebo tablets three times daily during the second, while the other group received the two treatments in the reverse order.

Observations and measurements

Prior to entry into the study all patients received a thorough clinical examination, including disease history and laboratory tests, and underwent a battery of vestibulo-

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metric tests (using electronystagmography) and audiometry. Patients were then allocated to one of three diagnostic categories: Menière's disease, other specified types of peripheral vertigo, or peripheral vertigo of unknown origin. The diagnosis of Menière's disease was reserved for patients with a combination of paroxysmal vertigo, tinnitus and varying hearing loss, with demonstrable recruitment on audiometric testing.

During the study period patients were given diary cards on which they were asked to record each day the nature, frequency and severity of their vertiginous complaints. At the end of each six-week treatment period the patients returned to the out-patient clinic and were questioned by the investigator on the overall status of their complaints during the previous six weeks. The following items were rated at these visits using a numerical scoring system:

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Vestibulometry and audiometry were also repeated at the end of each treatment period; at the end of the study, the investigator compared the results of the tests performed at the end of week six with those from week 12.

At the end of the study both the investigator and the patient were asked to compare the overall condition of the patient's vertigo during the two treatment periods by choosing one of the following statements:

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—first period slightly better.
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Results

Twenty-seven patients entered the study, three of whom failed to complete the full 12 weeks (see Table I). The results in these three patients have been excluded from the statistical analysis of efficacy. Of the remaining 24 patients, 11 received placebo treatment first and 13 received betahistine first. The pre-treatment comparability of the two groups was good, both with respect to demographic data and the results of the various pre-treatment assessments (Table II).

Data on the efficacy of the two treatments were derived from two sources; the patient diary cards, and the assessments at the end of each treatment period. Adequately completed diary cards are available for 15 of the 24 patients included in the analysis. The data on these cards (Table III) reveal that statistically, both the incidence and severity of dizziness were significantly lower during betahistine treatment than during placebo ($p = 0.004$). The occurrence of nausea and vomiting was also significantly reduced during betahistine treatment ($p = 0.014$ and 0.036 respectively).

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These results show betahistine treatment to be useful in treating dizziness of unspecified peripheral vestibular origin. It is possible that an even more impressive response would be achieved with a higher daily dose of betahistine (author's opinion).

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The occurrence of nausea and vomiting was also significantly reduced during betahistine treatment ($p = 0.014$ and 0.036 respectively). There were no statistically significant differences in the results of audiometric or vestibulometric tests, or in the severity of tinnitus or deafness, between the two treatment periods. The overall comparisons of the two periods made by both the patients and the investigator were significantly in favour of betahistine ($p<0.001$). All diagnostic groups responded favourably to betahistine, confirming the efficacy of betahistine in the symptomatic treatment of peripheral vestibular vertigo. No unwanted signs or symptoms were reported.

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Clin. Otolaryngol. 1987, **12**, 131–135

Effect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study

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OOSTERVELD W. J. (1987) *Clin. Otolaryngol.* **12**, 131–135

Effect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study

The effect of betahistine on vestibular nystagmus induced by means of a torsion swing was tested in 10 subjects. Each individual received, in a randomized double-blind study, 3 different single oral dosages of betahistine (8, 16 and 32 mg) on 3 different occasions. Electronystagmographic tracings were taken at different time-intervals after drug intake. At 3–4 hours after a dose of 8 mg betahistine the nystagmus duration was reduced by 35%, after 16 mg betahistine by 48% and after 32 mg betahistine by 59% (mean values). All these differences in dose-response are highly significant ($P < 0.0005$). It can be concluded from these results, that a dose of 3×8 mg or 3×16 mg betahistine daily will be efficacious in maintenance treatment of vertigo, and a dose of 3×24 mg betahistine daily will have even more effect.

Keywords *betahistine vertigo treatment vestibular function*

In several double blind placebo controlled clinical studies[1–5] betahistine has been proved to be effective in the treatment of patients suffering from episodes of peripheral vertigo, such as are present in Ménière's disease. The doses used in these studies ranged from 24 to 48 mg betahistine daily. Clinical observations suggested that a dose of 72 mg (3×24 mg) betahistine daily might be even more effective in the treatment of these patients. The aim of the present study was to find objective support for this impression.

Methods

VOLUNTEERS

Ten normal subjects, 6 males and 4 females between 23 and 30 years of age, volunteered to participate in the study. They all had a history free from neurological and cochleovestibular pathology. All of them received 3 different single oral doses of betahistine on 3 different occasions with an inter-test interval of 1 week. The sequence of the dose strength was randomized. Betahistine (8, 16 and 32 mg) was supplied in individually coded opaque capsules of identical appearance.

VESTIBULAR NYSTAGMUS

Vestibular nystagmus was induced by means of a torsion swing, the oscillations provoking alternating angular accelerations in the swing and in the subject sitting on it. These accelerations stimulate the horizontal semicircular canals of the vestibular organ, resulting in nystagmus in the horizontal plane. This nystagmus can

* Trade marks: Serc®, Betaserc®, Vasomotal®.

be recorded electronystagmographically. Each time the torsion swing test is repeated in a subject, the provoked nystagmus will be the same, if the initial amplitude of the swing movement is kept constant.

If a drug known to reduce vestibular reflexes has been administered, the parameters characteristic for the nystagmus will change. The most relevant ENG parameters are the duration of nystagmus, the speed of the slow component and the frequency. The duration of the slow nystagmus phase was used in the present study.

During the study, the oscillation time of the swing was 16 seconds; this time remained constant at each test point and the average duration of nystagmus for each individual was calculated from 20 measurements at each test point. The average duration in the torsion swing test performed before drug administration was taken as 100% in each individual subject.

The duration of nystagmus, following drug administration, was calculated as a percentage of the pre-treatment duration. The duration of nystagmus was measured before administration of the drug and at ½, 1, 2, 3, 4, 6 and 8 h after. This method has also been used in previous experiments with other drugs.[6-8]

STATISTICS

The following statistical tests were used: Wilcoxon matched-pair signed-rank test, and Pearson's correlation coefficient. A two-tailed *P*-value of less than 0.05 was regarded as being statistically significant.

Results

Ten volunteers received a single oral dose of betahistine (8, 16 or 32 mg) in a randomized and double-blind fashion, on 3 different occasions with an inter-test interval of 1 week. The absolute values of the duration of nystagmus at the onset of each investigation are listed in Table 1.

It is clear that the 3 values before administration of the drug for each subject are very similar, the standard error of the mean (SEM) is less than 0.7% for all subjects. Table 1 revealed no significant differences in the absolute values of the nystagmus duration at the onset of the investigation.

TIME-INTENSITY

The mean courses of the duration of nystagmus with respect to time, induced by the 3 different dosages of betahistine in the 10 volunteers, are plotted in Figure 1. This shows that betahistine significantly reduces the duration of nystagmus when given in doses of 8 mg, 16 mg and 32 mg ($P < 0.0005$) and that the higher the dose the more marked is the reduction in the duration of the nystagmus (again $P < 0.0005$).

DOSE-RESPONSE

For each volunteer the lowest values of the duration of nystagmus at the 3 different doses were listed and also the time (t_{max}) after administration of the drug at which these lowest values occurred. By subtracting the lowest value from the baseline value (= 100%) the maximal reduction of the nystagmus duration, induced by the 3 different doses in the 10 subjects, could be determined (see Table 2).

The results showed that 16 mg betahistine was more effective ($P < 0.0005$) in reducing the nystagmus duration (mean reduction 48%) than 8 mg betahistine (mean reduction 35%). Further, 32 mg betahistine was more effective ($P < 0.0005$) (mean reduction 59%) than 16 mg betahistine.

The time-interval between drug intake and the maximal effect (t_{max}) was significantly shorter ($P < 0.005$) after a dosage of 8 mg betahistine than after 16 or 32 mg betahistine. The t_{max} between the dosage of 16 and 32 mg betahistine (Table 2) was not significantly different.

The reduction of the duration of

Table 1. Nystagmus duration on torsion swing test before betahistine (blank values)

	Duration of nystagmus(s)				
Test subject	*8 mg*	*16 mg*	*32 mg*	*Mean*	*SEM*
1	9.51	9.59	9.61	9.57	0.03
2	9.45	9.47	9.43	9.45	0.01
3	10.11	9.98	10.21	10.10	0.07
4	9.63	9.61	9.57	9.60	0.02
5	9.67	9.62	9.63	9.64	0.02
6	9.58	9.63	9.56	9.59	0.02
7	10.05	9.95	10.03	10.01	0.03
8	9.38	9.43	9.39	9.40	0.02
9	9.84	9.81	9.78	9.81	0.02
10	10.39	10.37	10.41	10.39	0.01
Mean	9.76	9.75	9.76	—	—
s.d.	0.34	0.29	0.33	—	—
SEM	0.11	0.09	0.10	—	—

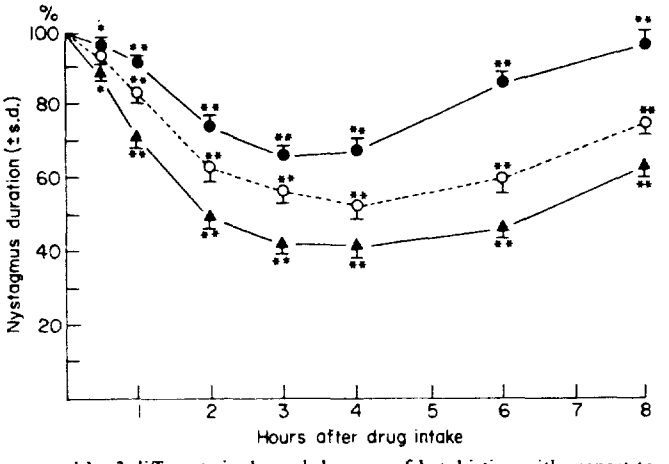

Figure 1. Reduction of nystagmus duration caused by 3 different single oral dosages of betahistine with respect to time in 10 volunteers (mean values ± s.d.). $n = 10$. * = $P < 0.05$; ** = $P < 0.0005$; ●——● = 8 mg; ○- - - -○ = 16 mg; ▲——▲ = 32 mg.

Table 2. The maximal reduction of the duration of nystagmus and the time this maximal effect occurred after drug intake

	8 mg betahistine		*16 mg betahistine*		*32 mg betahistine*	
Subject	t_{max} *(h)*	*reduction (%)*	t_{max} *(h)*	*reduction (%)*	t_{max} *(h)*	*reduction (%)*
1	3	38	4	47	4	55
2	4	41	4	53	4	57
3	3	41	3–4	46	4	61
4	3	31	4	44	4	63
5	3	33	4	50	3	62
6	3	34	4	45	4	59
7	3	32	4	50	4	58
8	3	37	4	51	4	62
9	3	34	4	46	4	58
10	3–4	31	4	48	3	56
Mean	3.2	35*	4.0†	48	3.8†	59*
s.d.	0.3	3.8	0.2	2.9	0.4	2.8
SEM	0.1	1.2	0.05	0.9	0.1	0.9

* Wilcoxon $P < 0.0005$, compared with reducing properties of 16 mg betahistine.
† Wilcoxon $P < 0.005$, compared with t_{max} after 8 mg betahistine.

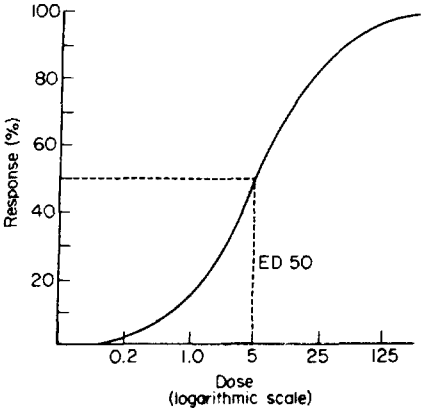

Figure 2. A log dose-response (LDR) curve. The horizontal axis shows the dose on a logarithmic scale. The curve shows the relationship between the dose and the percentage of the maximal response induced by this dose.

nystagmus was plotted in a log dose-response curve. A log dose-response (LDR) curve is an S-shaped curve with a linear part in the middle (see Figure 2). The ED_{50} is the dose which causes 50% of the maximal effect.

Semi-logarithmic curve fitting of all 30 test-values (see Table 2), revealed a high correlation ($r = 0.95$) between these test-values. Therefore these test-values must be on the linear part of the LDR curve and the maximal effect on reduction of nystagmus duration induced by a single dose of betahistine must be reached at a dosage over 32 mg ($P < 0.0005$). These results are shown in Figure 3.

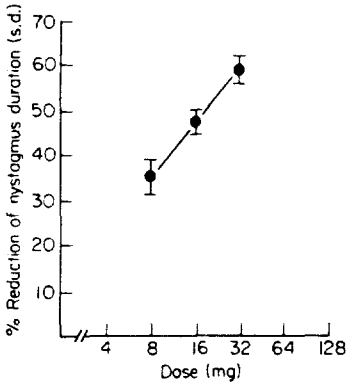

Figure 3. The maximal effect of 3 different single oral doses of betahistine on nystagmus duration in 10 volunteers: a part of the log dose-response curve. $n = 10$; $y = a + b \ln x$: ($a = -0.37$, $b = 17.2$); $r = 0.95$; $P < 0.005$.

Discussion

Vestibular nystagmus induced by means of a torsion swing, proved to be an excellent objective method of studying the effect of different doses of betahistine on the duration of nystagmus in humans. The present study has demonstrated that betahistine is undoubtedly potent in reducing this duration (up to 63% reduction in this study). All 3 doses of betahistine had a clear effect on the duration of nystagmus, but the single dose of 32 mg betahistine proved to be more effective than 16 mg betahistine, the latter dose being in turn more effective than 8 mg betahistine. The nystagmus duration reducing properties of the 3 dosages lie on the linear part of the log dose-response curve (see Figure 3), therefore the maximal effect of betahistine on nystagmus duration can be expected to occur following a single dose of over 32 mg and this maximal effect occurred 3–4 h after drug intake. The volunteers reported no side-effects. From these results it can be concluded that 3×8 mg or 3×16 mg betahistine daily will be efficacious in the maintenance treatment of vertigo, but that a dosage of 3×24 mg betahistine daily will have even more effect. It is unlikely that the maximal effect of betahistine on vertigo is reached at a dosage of 3×24 mg daily.

A comparison with the results from previous experiments[6-8] indicates that the effect of 8 mg betahistine on reduction of nystagmus duration is similar to that of the antihistamines meclozine, chlorcyclizine, cinnarizine (15 and 45 mg) and flunarizine (10 and 30 mg). Betahistine, however, has no sedating properties. The effects of 16 and 32 mg betahistine are more pronounced than those of the antihistamines.

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A. INGREDIENT NAME:

BISMUTH CITRATE

B. Chemical Name:

C. Common Name:

Bismuthi et Ammonii Citras

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Results)	*(Specifications)*
Bismuth oxide content on dry basis	57.3%	55.0-59.0%

E. Information about how the ingredient is supplied:

A white, amorphous or micro-crystalline powder, odorless and tasteless, and permanent in the air.

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Hopkins, R. J. Current FDA-approved treatments for Helicobacter pylori and the FDA approval process. *Gastroenterology,* 1997; 113(6Suppl): S126-130.

Stanescu, A., Mayer, D., and Gabard, B. Helicobacter pylori eradication therapy with bismuth citrate/amoxycillin combination therapy. *Leber, Magen, Darm,* 1996; 26(1): 32-36.

Tillman, L. A., Drake, F.M., and Dixon, J. S. Review article: safety of bismuth in the treatment of gastrointestinal diseases. *Alimentary Pharmacology & Therapeutics,* 1996; 10(4): 459-467.

H. Information about dosage forms used:

Tablets

I. Information about strength:

120 mg, 2 tablets-3 times a day/ or Ranitidine bismuth citrate (RBC) 200, 400, 800mg bid.

J. Information about route of administration:

Orally

K. Stability data:

Melts at decomposition or with mineral acids
Stable

L. Formulations:

Bismuth Subnitrate.....100gms
Citric Acid.....70gms
Distilled water, a significant quantity
See file for compounding formulation

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

PRODUCT: BISMUTH CITRATE BATCH: 97235018 30-20 #552

WEIGHT: 25,0 kg Nº OF DRUMS: 1 Nº OF OPERATION: 11974285

SPECIFICATIONS: BPC-49

DETERMINATIONS	RESULTS	SPECIFICATIONS
Appearance	Correct	White powder
Identification	Complies	Bismuth Citrate
Solubility	Pass Test	Test
Bismuth oxide content on dry basis	57.3 %	55.0 - 59.0 %
Nitrates	Pass Test	Test
Chloride	Correct	< 500 ppm
Sulphate	Pass Test	Test
Copper	Pass Test	Test
Silver	Pass Test	Test
Lead	Pass Test	Test
Arsenic	Correct	< 2 ppm
Alkalis and Alkaline earths	Correct	< 0.5 %

Date manufacturing: 18 / 7 / 97 Canovelles, 20 / 11 / 97 12/97

Date expedition: 20 / 11 / 97

QUALITY CONTROL REPORT

CHEMICAL NAME.: BISMUTH CITRATE :_____

MANUFACTURE LOT NO.: 97235018

PHYSICAL TEST

SPECIFICATION TEST STANDARE.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE CRYSTALLINE POWDER.IS ODORLESS.

2) SOLUBILITY.:
SOLUBLE IN AMMONIA OR ALKALI CITRATES;INSOLUBLE IN WATER;SLIGHTLY SOLUBLE IN ALCOHOL.

K

3) MELTING POINT.:
MELTS AT DECOMPOSITION OR WITH MINERAL ACIDS.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) A SOLUTION RESPONDS TO THE TESTS FOR BISMUTH AND CITRATE.

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

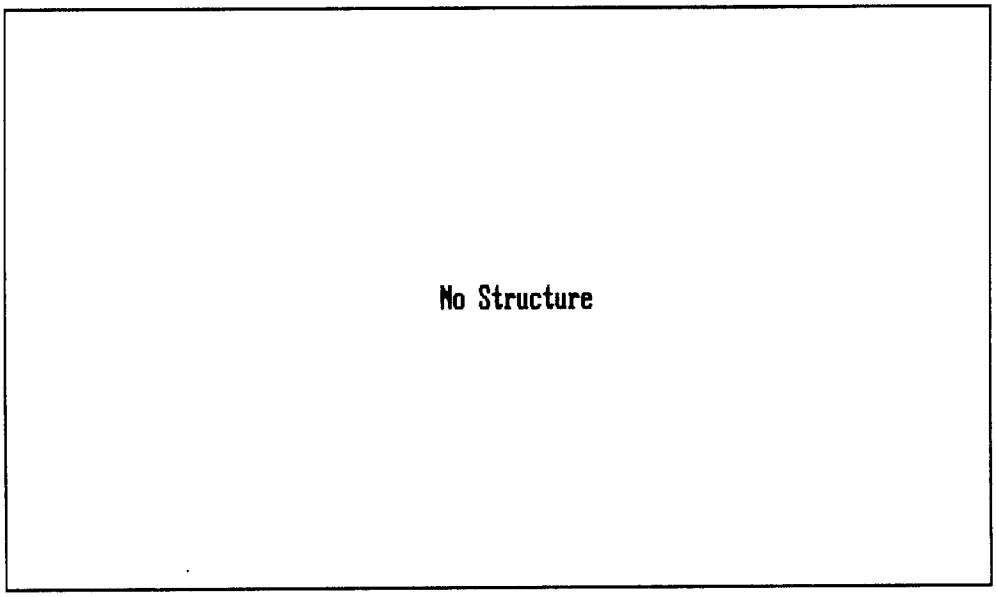
RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

MATERIAL SAFETY DATA SHEET

Sigma-Aldrich Corporation
1001 West Saint Paul Ave, Milwaukee, WI 53233 USA

id 5/92- 7/92

		Sigma	Aldrich
For Emergency	Contact USA/Canada	800-325-5832	800-231-8327
	Outside USA/Canada	314-771-5765	414-273-3850



---------- IDENTIFICATION ----------

PRODUCT #: B1654 NAME: BISMUTH CITRATE
CAS #: 813-93-4
MF: C18H15BIO21

---------- TOXICITY HAZARDS ----------

DATA NOT AVAILABLE

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.
CAUSES EYE AND SKIN IRRITATION.
REPEATED EXPOSURE CAN CAUSE:
DAMAGE TO THE KIDNEYS
THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

CHRONIC EFFECTS

SYMPTOMS OF CHRONIC BISMUTH TOXICITY IN HUMANS CONSISTS OF DECREASED APPETITE, WEAKNESS, RHEUMATIC PAIN, DIARRHEA, FEVER, METAL LINE ON THE GUMS, FOUL BREATHE, GINGIVITIS AND DERMATITIS. JAUNDICE AND CONJUNCTIVAL HEMORRHAGE ARE RARE, BUT HAVE BEEN REPORTED. BISMUTH NEPHROPATHY WITH PROTEINURIA MAY OCCUR. THE KIDNEY IS THE SITE OF HIGHEST CONCENTRATION WITH THE LIVER BEING CONSIDERABLY LOWER. BISMUTH DOES PASS INTO THE AMNIOTIC FLUID AND INTO THE FETUS.

FIRST AID

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.

IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.

---------- PHYSICAL DATA ----------

SPECIFIC GRAVITY: 3.458

SOLUBILITY: AMMONIA SOLUTION: SOLUBLE WATER-SLIGHTLY SOLUBLE

APPEARANCE AND ODOR

SOLID.

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.

---------- REACTIVITY DATA ----------

STABILITY

STABLE. K

CONDITIONS TO AVOID

MAY DISCOLOR ON EXPOSURE TO LIGHT.

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

MECHANICAL EXHAUST REQUIRED.

AVOID BREATHING DUST.

IRRITATING TO EYES AND SKIN.

IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.

WEAR SUITABLE PROTECTIVE CLOTHING.

TARGET ORGAN(S):

KIDNEYS

KEEP CONTAINER CLOSED. USE WITH ADEQUATE VENTILATION.

BENZINUM.

BENZIN.

[PETROLEUM BENZIN. PETROLEUM ETHER.]

A purified distillate from American petroleum, consisting of hy carbons, chiefly of the marsh-gas series [C_5H_{12}, C_6H_{14}, and homolo compounds].

Benzin should be carefully kept in well-stoppered bottles or tin in a cool place, remote from lights or fire.

A transparent, colorless, diffusive liquid, of a strong, characteristic slightly resembling that of petroleum, but much less disagreeable, and a neutral reaction.

Specific gravity: 0.670 to 0.675 at 15° C. (59° F.).

Boiling point: 50° to 60° C. (122° to 140° F.).

Insoluble in water; soluble in about 6 parts of alcohol, and readily in ether, chloroform, benzol, and fixed and volatile oils.

Benzin is highly inflammable, and its vapor, when mixed with a ignited, explodes violently.

On evaporating Benzin from the hand, it should leave no odor, and o orating it from a warmed dish, it should leave no residue (absence of *hydrocarbons*).

When it is boiled for a few minutes with one-fourth its volume of s ammonia, and a few drops of silver nitrate T.S., the ammoniacal liquid not turn brown (absence of *pyrogenous products* and *sulphur compounds*).

If 5 drops of Benzin be added to a mixture of 40 drops of sulphuric drops of nitric acid, in a test-tube, the liquid warmed for about ten m and then set aside for half an hour, on diluting it, in a shallow dis water, it should not evolve the bitter-almond-like odor of nitro-benzol ence from, and absence of, *benzol*).

BENZOINUM.

BENZOIN.

A balsamic resin obtained from *Styrax Benzoin* Dryander (na *Styraceæ*).

In lumps consisting of agglutinated, yellowish-brown tears, which a nally milk-white, or in the form of a reddish-brown mass, more or les from whitish tears imbedded in it. It is almost wholly soluble in 5 moderately warm alcohol, and in solutions of the fixed alkalies. When it gives off fumes of benzoic acid. It has an agreeable, balsamic od slight, aromatic taste.

Preparations: Adeps Benzoinatus. Tinctura Benzoini. Tinctura Ti Composita.

BISMUTHI CITRAS.

BISMUTH CITRATE.

$BiC_6H_5O_7 = 397.44$.

Bismuth Subnitrate, *one hundred grammes*	10
Citric Acid, *seventy grammes*	7
Distilled Water, *a sufficient quantity.*	

BENZINUM.

BENZIN.

:OLEUM BENZIN. PETROLEUM ETHER.]

llate from American petroleum, consisting of hyd
: the marsh-gas series [C_5H_{12}, C_6H_{14}, and homolog

)e carefully kept in well-stoppered bottles or tin c
)emote from lights or fire.

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ing that of petroleum, but much less disagreeable, and ha
)n.
ty: 0.670 to 0.675 at 15° C. (59° F.).
: 50° to 60° C. (122° to 140° F.).
water; soluble in about 6 parts of alcohol, and readily sol
)form, benzol, and fixed and volatile oils.
ghly inflammable, and its vapor, when mixed with air
es violently.
ng Benzin from the hand, it should leave no odor, and on
1 a warmed dish, it should leave no residue (absence of

)oiled for a few minutes with one-fourth its volume of spi
a few drops of silver nitrate T.S., the ammoniacal liquid
n (absence of *pyrogenous products* and *sulphur compounds*).
f Benzin be added to a mixture of 40 drops of sulphuric
: a[illegible] a test-tube, the liquid warmed for about ten mi
asi[illegible] half an hour, on diluting it, in a shallow dish
ld n[illegible]volve the bitter-almond-like odor of nitro-benzol
d absence of, *benzol*).

BENZOINUM.

BENZOIN.

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varm alcohol, and in solutions of the fixed alkalies. When
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itic taste.

Adeps Benzoinatus. Tinctura Benzoini. Tinctura Be

BISMUTHI CITRAS.

BISMUTH CITRATE.

$BiC_6H_5O_7 = 397.44$.

Subnitrate, *one hundred grammes* 100
d, *seventy grammes* 70
Water, *a sufficient quantity.*

Boil the Bismuth Subnitrate and the Citric Acid with *four hundred* (400) *cubic centimeters* of Distilled Water for about fifteen minutes, or until a drop of the mixture yields a clear solution with ammonia water. Then add *five thousand* (5000) *cubic centimeters* of Distilled Water, allow the suspended matter to deposit, wash the precipitate, first by decantation, and afterwards on a strainer, with Distilled Water, until the washings are tasteless, and dry the residue at a gentle heat.

A white, amorphous or micro-crystalline powder, odorless and tasteless, and permanent in the air.

Insoluble in water or alcohol, but soluble in ammonia water, and in solutions of the citrates of the alkalies.

When strongly heated, the salt chars, and, on ignition, leaves a more or less blackened residue having a yellow surface, and soluble in warm nitric acid. This solution, when dropped into water, occasions a white turbidity.

A solution of the salt in ammonia water, when treated with hydrogen sulphide in excess, yields a black precipitate.

If the filtrate from the latter be deprived by heat of the excess of hydrogen sulphide and cooled, a portion of it, boiled with lime water, yields a white precipitate.

If another portion of the cooled filtrate be mixed with an equal volume of concentrated sulphuric acid, and again cooled, no brown or brownish-black color should appear around a crystal of ferrous sulphate dropped into the liquid (limit of *nitrate*).

Preparation: Bismuthi et Ammonii Citras.

BISMUTHI ET AMMONII CITRAS.

BISMUTH AND AMMONIUM CITRATE.

Bismuth Citrate, *one hundred grammes* ..... 100 Gm.
Ammonia Water,
Distilled Water, each, *a sufficient quantity.*

Mix the Bismuth Citrate with *two hundred* (200) *cubic centimeters* of Distilled Water to a smooth paste, heat the mixture on a water-bath, and gradually add Ammonia Water, until the salt is dissolved, and the liquid is neutral or has only a faintly alkaline reaction. Then filter the solution, evaporate it on a water-bath to a syrupy consistence, and spread it upon plates of glass, so that, when dry, the salt may be obtained in scales.

Keep the product in small, well-stoppered bottles, protected from light.

Small, shining, pearly or translucent scales, odorless, having a slightly acidulous and metallic taste, and becoming opaque on exposure to the air.

Very soluble in water, and but sparingly soluble in alcohol.

When strongly heated, the salt fuses, and finally leaves a more or less blackened residue, having a yellow surface, and soluble in warm nitric acid. This solution, when dropped into water, occasions a white turbidity.

The aqueous solution of the salt is neutral or faintly alkaline to litmus paper.

Uses and Administration continued

colon. A complex of bisacodyl with tannic acid (bisacodyl tannex) is generally used in a dose equivalent to 1.5 to 3.0 mg of bisacodyl dissolved in 1 litre of barium sulphate suspension. The total dose for one procedure should not exceed 4.5 mg of bisacodyl and no more than 6 mg should be administered in 72 hours.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

BP 1993: Bisacodyl Suppositories; Bisacodyl Tablets;
USP 23: Bisacodyl Suppositories; Bisacodyl Tablets.

Proprietary Preparations

Aust.: Dulcolax; Laxbene; *Austral.:* Bisalax; Durolax; *Belg.:* Dulcolax; Purgo-Pil; *Canad.:* Bisacolax†; Dulcolax; *Fr.:* Contalax; Dulcolax; *Ger.:* Agaroletten N; Bisco-Zitron†; Drix; Dulcolax; Florisan N; Laxanin N; Laxans-ratiopharm†; Laxbene; Laxbene N; Laxoberal Bisa; Logomed Abführ-Dragees; Mandrolax; Multilax†; Nedalax†; Pyrilax; *Stadalax†; tempolax; Vinco-Abführperlen; Ital.:* Alaxa; Dulcolax; Normalene; *Neth.:* Dulcolax; Nourilax†; Toilax†; Zwitsalax/N; *Norw.:* Dulcolax; Toilax; *S.Afr.:* Capolax; Dulcolax; Megalax; Perilax†; *Spain:* Dulco Laxo; Medesup; *Swed.:* Dulcolax; Toilax; *Switz.:* Demolaxin; Dulcolax; Ercolax; Laxbene†; Muxol; Prontolax; *UK:* Dulco-Lax; *USA:* Bisco-Lax; Dulcagen; Dulcolax; Evac-Q-Kwik Suppository; Fleet Bisacodyl; Fleet Laxative.

Multi-ingredient preparations. *Aust.:* Laxbene; Prepacol; Purgazen; Purigoa; *Austral.:* Coloxyl; Durolax X-Pack; Raykit; *Belg.:* Prepacol; Softene; *Canad.:* Dulcodos†; Evac-Q-Kwik; Royvac Kit; *Fr.:* Néo-Boldolaxine; Pilule Dupuis; Prépacol; *Ger.:* Bekunis†; Daluwal Forte†; Dragees Duesberg†; Mediolax N; Milkitten Abführdragees; Milkitten S†; Potsilo; Prepacol; Regulat†; Rheolind†; Tirgon†; Vinco V; *Ital.:* Fisiolax; *Spain:* Bekunis Complex; Boldolaxin; *Switz.:* Aloïnophen; Bekunis; Drix; Tirgon; *UK:* Nylax; *USA:* Dulcolax Bowel Prep Kit; Tridrate Bowel Evacuant Kit; X-Prep Bowel Evacuant Kit-1; X-Prep Bowel Evacuant Kit-2.

Bismuth Compounds (17157-z)

Bismuth compounds have been used for their antacid and astringent properties in a variety of gastro-intestinal disorders, and have been applied topically in skin disorders and anorectal disorders such as haemorrhoids. Certain salts, notably tripotassium dictratobismuthate and to a lesser extent bismuth salicylate, are used in the treatment of peptic ulcer. Most of the bismuth compounds in current use are poorly soluble, which reduces their toxicity, but excessive or prolonged use may lead to bismuth accumulation and toxicity, including renal failure, liver damage, and encephalopathy.

Bismuth (5265-w)

Bi = 208.98037.
CAS — 7440-69-9.

A silvery-white crystalline brittle metal with a pinkish tinge.

Bismuth Aluminate (5268-y)

Bismuth Aluminate *(USAN).*

Aluminum Bismuth Oxide.

$Bi_2(Al_2O_4)_3.10H_2O$ = 952.0.
CAS — 12284-76-3 (anhydrous bismuth aluminate).

Pharmacopoeias. In *Fr.*

Practically **insoluble** in water.

Bismuth Citrate (14763-y)

CAS — 813-93-4.

Practically **insoluble** in water and in alcohol; soluble in solutions of alkali citrates.

Bismuth Oxide (5271-p)

Bismuth Trioxide.

Bi_2O_3 = 466.0.
CAS — 1304-76-3.

Practically **insoluble** in water.

Bismuth Phosphate (18850-r)

$BiPO_4$ = 304.0.
CAS — 10049-01-1.

Pharmacopoeias. In *Fr.*

Slightly **soluble** in water and in dilute acids; practically insoluble in alcohol and in acetic acid; **soluble** in concentrated nitric acid and in concentrated hydrochloric acid.

Bismuth Salicylate (5275-l)

Basic Bismuth Salicylate; Bismuth Oxysalicylate; Bismuth Subsalicylate *(USAN).*

CAS — 14882-18-9.

Pharmacopoeias. In *Fr., Hung., It.,* and *Neth.*

A basic salt of varying composition, corresponding approximately to $C_6H_4(OH).CO_2(BiO)$ and containing about 58% of Bi.

Bismuth Subcarbonate (5279-c)

Bismuth Subcarbonate (USAN).

Basic Bismuth Carbonate; Basisches Wismutkarbonat; Bism. Carb.; Bismuth Carbonate; Bismuth Oxycarbonate; Bismuthi Subcarbonas; Bismutylum Carbonicum; Carbonato de Bismutila.

CAS — 5892-10-4 (anhydrous bismuth subcarbonate); 5798-45-8 (bismuth subcarbonate hemihydrate).

Pharmacopoeias. In *Aust., Belg., Br., Chin., Cz., Eur., Fr., Ger., It., Neth.,* and *Port.*

The standards of *Ph. Eur.* apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

A white or almost white odourless powder.

Practically **insoluble** in water, in alcohol, and in ether; dissolves in mineral acids with effervescence. **Protect** from light.

Bismuth Subgallate (5280-s)

Bismuth Subgallate *(USAN).*

Basic Bismuth Gallate; Basisches Wismutgallat; Bism. Subgall.; Bismuth Oxygallate; Bismuthi Subgallas.

$C_7H_5BiO_6$ = 394.1.
CAS — 99-26-3.

Pharmacopoeias. In *Fr., Ger., Hung., Jpn, Neth.,* and *US.*

USP specifies 52 to 57% of Bi_2O_3 when dried at 105° for 3 hours. It is an odourless amorphous bright yellow powder. Practically **insoluble** in water, in alcohol, in chloroform, in ether, and in very dilute mineral acids; dissolves readily with decomposition in warm, moderately dilute hydrochloric, nitric, or sulphuric acids; readily dissolves in solutions of alkali hydroxides to form a clear yellow liquid which rapidly becomes deep red. **Store** in airtight containers. Protect from light.

Bismuth Subnitrate (5281-w)

Basic Bismuth Nitrate; Basisches Wismutnitrat; Bism. Subnit.; Bismuth Hydroxide Nitrate Oxide; Bismuth Oxynitrate; Bismuth (Sous-Nitrate de) Lourd; Bismuthi Subnitras; Bismuthyl Nitrate; Magistery of Bismuth; Nitrato de Bismutilo; Subazotato de Bismuto; White Bismuth.

$Bi_6O(OH)_9(NO_3)_4$ = 1462.0.
CAS — 1304-85-4.

Pharmacopoeias. In *Aust., Cz., Fr., Ger., Hung., Jpn,* and *US.*

Fr. also includes Bismuth (Sous-Nitrate de) Léger (*Bismuthi Subnitras Levis*) which is described as a variable mixture of bismuth hydroxide, carbonate, and subnitrate.

USP specifies not less than 79% of Bi_2O_3 calculated on the dried basis. It is a white slightly hygroscopic powder. Practically **insoluble** in water and in alcohol; readily dissolves in nitric and hydrochloric acids.

Bismuth Tannate (11269-r)

Practically **insoluble** in water, in alcohol, and in ether.

Bismuth Tribromphenate (5282-e)

Bismuth Tribromophenate; Bismutum Tribromophenylicum; Bromphenobis; Bromphenol Bismuth; Xeroformium.

CAS — 5175-83-7.

Slightly **soluble** in water, in alcohol, in chloroform, and in vegetable oils.

Tripotassium Dicitratobismuthate (3778-t)

Bismuth Subcitrate; Colloidal Bismuth Subcitrate.

CAS — 57644-54-9.

Adverse Effects, Treatment, and Precautions

The bismuth compounds listed above are insoluble or very poorly soluble, and bismuth toxicity does not currently appear to be common with them if they are used as they are now for limited periods. However, excessive or prolonged dosage may produce symptoms of bismuth poisoning, and for this reason long-term systemic therapy is not recommended. Also it should not be forgotten that reversible encephalopathy was once a problem in some countries, notably France and Australia, and did not be related to dose or duration of use; both toxicity had also occurred, sometimes with the encephalopathy. This led to restr the use of bismuth salts and a virtual dis of these toxic effects.

Nausea and vomiting have been reporte ing or blackening of the faeces and tongu cur due to conversion to bismuth sulph gastro-intestinal tract.

The effects of acute bismuth intoxicatio gastro-intestinal disturbances, skin reacti matitis, and discoloration of mucous mem characteristic blue line may appear on t There may be renal failure and liver dama

Other adverse effects may not be related to muth content. With bismuth subnitrate giv there is a risk of the nitrate being reduced testines to nitrite and the development of m globinaemia. Absorption of salicylate following the administration of bismuth by mouth and therefore the adverse effe ment of adverse effects, and precautions (see p.17) should be considered.

Although bismuth salts such as tripotassium tobismuthate or bismuth salicylate are g tetracycline hydrochloride as part of 'triple (see below), they may inhibit the efficacy of clines taken by mouth and doses of the should be separated by as long as possible

Bismuth compounds should not be given with renal disorders.

Acute toxicity. Reviews[1,2] and reports[3-6] of bis ty.

1. *Winship KA. Toxicity of bismuth salts. Adverse Acute Poisoning Rev* 1983; **2:** 103–21.
2. Slikkerveer A, de Wolff FA. Pharmacokinetics and t bismuth compounds. *Med Toxicol Adverse Drug Exp* 303–23.
3. Morrow AW. Request for reports: adverse reaction muth subgallate. *Med J Aust* 1973; **1:** 912.
4. Martin-Bouyer G. Intoxications par les sels de bism istrés par voie orale: enquête épidémiologique. *The* **31:** 683–702.
5. Stahl JP, *et al.* Encéphalites au sel insoluble de bismu urs d'actualité. *Nouv Presse Med* 1982; **11:** 3856.
6. Von Bose MJ, Zaudig M. *Encephalopathy resembl* zfeldt-Jakob disease following oral, prescribed muth nitrate. *Br J Psychiatry* 1991; **158:** 278–80.

FOLLOWING TOPICAL APPLICATION. Encephalopathy associated with the use of bismuth iodoform (BIPP) for the packing of wound cavities after head and neck,[1] although there is some debate the bismuth or the iodoform component is respo

1. Wilson APR. The dangers of BIPP. *Lancet* 1994;
2. Roy P-M, *et al.* Dangers of bismuth iodoform pa *Lancet* 1994; **344:** 1708.

Interactions. Pretreatment with omeprazole about a threefold increase in absorption of tripotassium dicitratobismuthate in 6 healthy mean peak plasma concentration of bismuth follo gle dose of 240 mg of tripotassium dicitratobis increased from 36.7 to 86.7 ng per mL after co ministration, suggesting an increased risk of dual therapy. The mechanism was thought to be in gastric pH produced by the antisecretory. results had been reported with ranitidine.[2]

1. Treiber G, *et al.* Omeprazole-induced increase tion of bismuth from tripotassium dicitrato bism *Pharmacol Ther* 1994; **55:** 486–91.
2. Nwokolo. CU, *et al.* The effect of histamine H_2-rece ade on bismuth absorption from three ulcer-he pounds. *Gastroenterology* 1991; **101:** 889–94.

Overdosage. Bismuth salicylate or tripotassium bismuthate in recommended doses are rarely ass serious adverse effects but there are reports of re[3] encephalopathy,[4-6] and neurotoxicity[7] following chronic[4,6] overdose. Bismuth has been detected urine, stools, and kidneys of these patients; a blood tion of 1.6 µg per mL was found 4 hours after a d Chronic ingestion of clinical doses intermittently has been reported to cause paraesthesia, insomnia paired memory.[7] Encephalopathy has not been with recommended doses of tripotassium dicitrato but it has been suggested that if blood-bismuth c exceed 100 ng per mL, bismuth preparations sh continued.[8]

The optimal treatment of bismuth overdosage Gastric lavage, purgation, and hydration should

Database: Medline <1966 to present>

Set	Search	Results
1	exp bismuth/	2126
2	bismuth citrate.tw.	53
3	efficacy.tw.	108250
4	safety.tw.	44957
5	exp drug therapy/	115501
6	2 and 3	11
7	2 and 4	4
8	2 and 5	13
9	from 6 keep 3-5,7-8,10	6
10	from 7 keep 3-4	2
11	from 8 keep 12-13	2

<1>
Unique Identifier
98060676
Authors
Laine L. Estrada R. Trujillo M. Emami S.
Title
Randomized comparison of ranitidine bismuth citrate-based triple therapies for Helicobacter pylori.
Source
American Journal of Gastroenterology. 92(12):2213-5, 1997 Dec.
Abstract
OBJECTIVES: In an attempt to increase the efficacy and simplicity of FDA-approved regimens for Helicobacter pylori, we studied (1) addition of an inexpensive antibiotic (amoxicillin) to twice-daily ranitidine bismuth citrate (RBC)-clarithromycin dual therapy, and (2) substitution of RBC for bismuth subsalicylate + H2-receptor antagonist in bismuth-based triple therapy. METHODS: Subjects with previously untreated Helicobacter pylori infection documented by 13C-urea breath test plus either endoscopic biopsy or serology were randomly assigned to a 2-wk course of (1) RBC 400 mg b.i.d., amoxicillin 1 g b.i.d., and clarithromycin 500 mg b.i.d. (RAC), or (2) RBC 400 mg b.i.d., metronidazole 250 mg t.i.d., and tetracycline 500 mg t.i.d. (RMT). Repeat breath test was performed 4 wk after the completion of therapy. RESULTS: Intent-to-treat and per-protocol cure rates for RAC were 46 of 50 patients (92%) and 45 of 47 patients (96%); for RMT they were 40 of 50 patients (80%) and 37 of 42 patients

(88%). Study drugs were stopped due to side effects in three patients (6%) taking RAC and six patients (12%) taking RMT. CONCLUSIONS: Twice-daily RBC-based triple therapy with clarithromycin and amoxicillin produces Helicobacter pylori eradication rates over 90%, which is comparable to rates seen with proton pump inhibitor-based triple therapies. RBC also may be substituted for bismuth subsalicylate and an + H2-receptor antagonist in standard bismuth-based triple therapy.

<2>
Unique Identifier
98056756
Authors
Hopkins RJ.
Title
Current FDA-approved treatments for Helicobacter pylori and the FDA approval process.
Source
Gastroenterology. 113(6 Suppl):S126-30, 1997 Dec.
Abstract
U.S. Food and Drug Administration (FDA) approval of new drugs expands treatment options and serves as a "safety net" of well-documented efficacy and safety. The information provided in the package insert facilitates physician education and provides some assurance that marketing information is accurate. As of February 1997, three Helicobacter pylori regimes have been FDA-approved for eradication of H. pylori in infected patients with active duodenal ulcers. Regimen 1, omeprazole + clarithromycin (O/C), was supported by two multicenter, controlled studies with a 6-month follow-up. Eradication rates were 74% (n = 53; 95% confidence interval [CI], 62-85) and 64% (n = 61; 95% CI, 52-76). Twenty-five of 26 patients with failed eradication therapy who were taking O/C with clarithromycin-susceptible strains before treatment and who had pretreatment and posttreatment susceptibility tests performed developed clarithromycin resistance after treatment. Regimen 2, ranitidine-bismuth-citrate + clarithromycin, was supported by two multicenter, placebo-controlled studies with a 6-month follow-up. Eradication rates were 84% (n = 19; 95% CI, 60-96) and 73% (n = 22; 95% CI, 50-88). Insufficient pretreatment and posttreatment susceptibility data were collected to assess antimicrobial resistance. Regimen 3, bismuth subsalicylate + metronidazole + tetracycline + an H2-receptor antagonist, was supported by two pivotal literature-based studies. Eradication rates in patients

with duodenal ulcer were 82% (n = 51; 95% CI, 70-92) and 77% (n = 39; 95% CI, 61-89), respectively. When extrapolating the results of these three FDA-approved regimens to the clinical setting, particular aspects of the clinical trial should be kept in mind. These include the type of controls, primary end points used, population studied, and number and type of dropouts.

<3>
Unique Identifier
97450491
Authors
Williams MP. Hamilton MR. Sercombe JC. Pounder RE.
Title
Seven-day treatment for Helicobacter pylori infection: ranitidine bismuth citrate plus clarithromycin and tetracycline hydrochloride.
Source
Alimentary Pharmacology & Therapeutics. 11(4):705-10, 1997 Aug.
Abstract
BACKGROUND: Dual therapy with ranitidine bismuth citrate plus clarithromycin twice daily for 14 days is an effective regimen for eradicating Helicobacter pylori infection. AIM: To determine whether this regimen can be improved by the addition of a second antibiotic, tetracycline hydrochloride, whilst reducing the duration of treatment to 7 days. METHODS: Sixty-one out-patients were enrolled to this open treatment study. All had H. pylori infection, as determined by 13C-urea breath test and, for those undergoing endoscopy, by rapid urease test. Patients were treated with ranitidine bismuth citrate 400 mg. clarithromycin 500 mg and tetracycline hydrochloride 500 mg all twice daily for 7 days. Eradication of H. pylori was assessed by two separate 13C-urea breath tests, the first 28-68 days after the completion of treatment, the second 28-162 days later. H. pylori infection was considered cured if both tests were negative. RESULTS: All 61 patients were included in the intention-to-treat efficacy analysis. Successful eradication of H. pylori was achieved in 55/61 patients (90%; 95% CI; 82-98%). Fifty-nine out of sixty-one patients reported 100% compliance; one patient missed a single dose of medication and the other withdrew at 48 h due to nausea and vomiting. Minor adverse events were reported by 30/61 patients. CONCLUSION: One-week triple therapy with ranitidine bismuth citrate, clarithromycin and tetracycline, all twice daily, is a safe and well-tolerated regimen which eradicates H. pylori in 90% of infected

patients.

<4>
Unique Identifier
96384043
Authors
Peterson WL. Ciociola AA. Sykes DL. McSorley DJ. Webb DD.
Title
Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating H. pylori and reducing ulcer recurrence. RBC H. pylori Study Group [see comments].
Comments
Comment in: Aliment Pharmacol Ther 1996 Dec;10(6):1035
Source
Alimentary Pharmacology & Therapeutics. 10(3):251-61, 1996 Jun.
Abstract
AIM: To compare the efficacy of the coadministration of ranitidine bismuth citrate plus the antibiotic clarithromycin, with ranitidine bismuth citrate alone or clarithromycin alone for the healing of duodenal ulcers, eradication of H. pylori and the reduction of ulcer recurrence. METHODS: This two-phase, randomized, double-blind, placebo-controlled, multicentre study consisted of a 4-week treatment phase followed by a 24-week post-treatment observation phase. Patients with an active duodenal ulcer were treated with either ranitidine bismuth citrate 400 mg b.d. for 4 weeks plus clarithromycin 500 mg t.d.s. for the first 2 weeks; ranitidine bismuth citrate 400 mg b.d. for 4 weeks plus placebo t.d.s. for first 2 weeks; placebo b.d. for 4 weeks plus clarithromycin 500 mg t.d.s. for the first 2 weeks; or placebo b.d. for 4 weeks plus placebo t.d.s. for the first 2 weeks. RESULTS: Ulcer healing rates after 4 weeks of treatment were highest with ranitidine bismuth citrate plus clarithromycin (82%) followed by ranitidine bismuth citrate alone (74%; P = 0.373), clarithromycin alone (73%; P = 0.33) and placebo (52%; P = 0.007). Ranitidine bismuth citrate plus clarithromycin provided significantly better ulcer symptom relief compared with clarithromycin alone or placebo (P < 0.05). The coadministration of ranitidine bismuth citrate plus clarithromycin resulted in significantly higher H. pylori eradication rates 4 weeks post-treatment (82%) than did treatment with either ranitidine bismuth citrate alone (0%; P < 0.001), clarithromycin alone (36%; P = 0.008) or placebo (0%; P < 0.001). Ulcer recurrence rates 24 weeks

post-treatment were lower following treatment with ranitidine bismuth citrate plus clarithromycin (21%) compared with ranitidine bismuth citrate alone (86%; P < 0.001), clarithromycin alone (40%; P = 0.062) or placebo (88%; P = 0.006). All treatments were well tolerated. CONCLUSIONS: The coadministration of ranitidine bismuth citrate plus clarithromycin is a simple, well-tolerated and effective treatment for active H. pylori-associated duodenal ulcer disease. This treatment regimen effectively heals duodenal ulcers, provides effective symptom relief, eradicates H. pylori infection and reduces the rate of ulcer recurrence. The eradication of H. pylori infection in patients with recently healed duodenal ulcers is associated with a significant reduction in the rate of ulcer recurrence.

<5>
Unique Identifier
97006475
Authors
Wyeth JW. Pounder RE. Duggan AE. O'Morain CA. Schaufelberger HD. De Koster EH. Rauws EA. Bardhan KD. Gilvarry J. Buckley MJ. Gummett PA. Logan RP.
Title
The safety and efficacy of ranitidine bismuth citrate in combination with antibiotics for the eradication of Helicobacter pylori.
Source
Alimentary Pharmacology & Therapeutics. 10(4):623-30, 1996 Aug.
Abstract
BACKGROUND: Ranitidine bismuth citrate is a novel salt of ranitidine and a bismuth citrate complex. It has intrinsic antisecretory and anti-Helicobacter pylori activity, but monotherapy rarely eradicates H. pylori infection in man. AIM: A pilot study to investigate rates of H. pylori eradication achieved by co-prescription of ranitidine bismuth citrate with antibiotics, and to identify several regimens which would merit further investigation. METHOD: One hundred dyspeptic patients infected with H. pylori were randomly allocated to treatment with ranitidine bismuth citrate 800 mg b.d. plus either amoxycillin, metronidazole, clarithromycin, cefuroxime axetil, tetracycline, tetracycline plus metronidazole or clarithromycin plus tetracycline for 14 days. Eradication of infection was assessed using the 13C-urea breath test 4 weeks after the end of treatment. RESULTS: In a per protocol analysis eradication of H. pylori ranged between 22 and 100%; the

intention-to-treat eradication rates ranged between 15 and 92%. No adverse events were specifically attributed to ranitidine bismuth citrate. CONCLUSION: Co-prescription therapy, using ranitidine bismuth citrate and one or more antibiotics, is suitable for further investigation in large-scale clinical trials in patients infected with H. pylori.

<6>
Unique Identifier
97004564
Authors
Stanescu A. Mayer D. Gabard B. Jost G. Baczako K. Dragici A. Malfertheiner P.
Title
[Helicobacter pylori eradication therapy with bismuth citrate/amoxycillin combination therapy]. [German]
Source
Leber, Magen, Darm. 26(1):32-6, 1996 Jan.
Abstract
The efficacy of a new combination preparation containing bismuth citrate and amoxicillin in one tablet was compared with the efficacy of bismuth citrate monotherapy in a randomised double-blind study on the eradication of Helicobacter pylori. The study involved 70 H. pylori positive (antrum biopsies showing a positive urease test) patients with non-ulcer dyspepsia and chronic gastritis. The treatment period was 14 days; 35 patients in group 1 received 2 tablets tid containing the bismuth citrate amoxicillin combination (BIAM tablet; 250 mg amoxicillin base and 120 mg bismuth); 35 patients in group 2 were treated with 2 tablets tid containing bismuth citrate (BI tablet; 120 mg bismuth). Total daily dose was therefore 1500 mg amoxicillin + 720 mg bismuth in group 1 patients resp. 720 mg bismuth in group 2 patients. 4 weeks after therapy H. pylori could not be histologically detected in the antrum of 22 patients (63%) in group 1 and 8 patients (24%) in group 2. Thus in group 1 (BIAM) a significantly higher eradication rate ($p < 0.001$) was shown than in group 2 (BI). Inflammation characterized by the infiltration of polymorphonuclear cells was significantly ($p < 0.01$) less pronounced in group 1 (BIAM) than in group 2 (BI) 4 weeks after the end of treatment. Gastrointestinal distress was quantified by evaluation of 13 different symptoms using a fourpoints scale at the beginning of the study and after 2 and 6 weeks. The sum of scores decreased by 81% in group 1 (BIAM) and 71% in group 2 (BI) after 6 weeks.

Database: Medline <1966 to present>

Set	Search	Results
1	exp bismuth/	2126
2	bismuth citrate.tw.	53
3	efficacy.tw.	108250
4	safety.tw.	44957
5	exp drug therapy/	115501
6	2 and 3	11
7	2 and 4	4
8	2 and 5	13
9	from 6 keep 3-5,7-8,10	6
10	from 7 keep 3-4	2
11	from 8 keep 12-13	2
12	exp drug stability/	20813
13	2 and 12	0
14	stability.tw.	54760
15	2 and 14	0

<1>
Unique Identifier
97006457
Authors
Tillman LA. Drake FM. Dixon JS. Wood JR.
Title
Review article: safety of bismuth in the treatment of gastrointestinal diseases [see comments]. [Review] [60 refs]
Comments
Comment in: Aliment Pharmacol Ther 1996 Dec;10(6):1035-6
Source
Alimentary Pharmacology & Therapeutics. 10(4):459-67, 1996 Aug.
Abstract
Bismuth preparations are commonly used to treat a variety of gastrointestinal disorders, including peptic ulcers and dyspepsia. The safety profile of currently approved bismuth preparations, such as tripotassium dicitrato bismuthate (De-Nol), bismuth subsalicylate (Pepto-Bismol) and ranitidine bismuth citrate (Pylorid, Tritec), is excellent. Adverse reactions to these agents are mild, transient and infrequent, and reports of serious adverse reactions are rare. This, in part, reflects the low systemic bioavailability of bismuth from these medicines: less than 1% of the bismuth dose administered is absorbed. During

repeated dosing with ranitidine bismuth citrate 200, 400 or 800 mg b.d. trough plasma bismuth concentrations remain well below 50 micrograms/L. After 4 weeks of treatment median concentrations of 3.4 micrograms/L or less were reported amongst 1210 duodenal ulcer patients receiving this new chemical entity, while mean concentrations of 5.1 micrograms/L (plasma) and 12.3 micrograms/L (blood) have been reported in two studies of patients receiving tripotassium dicitrato bismuthate 120 mg q.d.s. for 4 weeks. Transient peak plasma bismuth concentrations greater than 50 micrograms/L are observed 30-60 min after dosing with tripotassium dicitrato bismuthate in some patients, but are not associated with any toxic effects. After discontinuation of treatment with bismuth preparations its excretion in urine may continue for up to 3 months, by which time blood bismuth concentrations have declined to pretreatment values. [References: 60]

<2>
Unique Identifier
95036730
Authors
Pounder RE.
Title
Treatment of peptic ulcers from now to the millennium. [Review] [61 refs]
Source
Baillieres Clinical Gastroenterology. 8(2):339-50, 1994 Jun.
Abstract
The present strategies for the management of peptic ulceration are well tolerated and clinically effective. Histamine H2-receptor antagonists can be used for mild to moderate disease, and proton pump inhibitors are of particular benefit for patients with severe peptic ulceration and the Zollinger-Ellison syndrome. However, none of these treatments provides protection against recurrent ulceration, except when taken as long-term continuous treatment. Long-term exposure to pharmacological agents raises problems of safety, particularly relating to a lack of intragastric acidity. In addition, the accelerated development of atrophic gastritis in patients receiving omeprazole requires investigation and assessment. It is unlikely that there will be any major development in the area of control of gastric acid secretion, except perhaps the introduction of specific immunization against gastrin. However, the clinical benefit of this strategy awaits assessment. The main area for development must be

the introduction of convenient and effective regimens for the eradication of Helicobacter pylori infection. Existing regimens are either simpler and relatively ineffective, or too complicated for widespread application. Bearing in mind the long gestation period of any new drug, it seems likely that the only innovative drug that will be introduced for the management of peptic ulceration before the millennium will be ranitidine bismuth citrate, an antisecretory anti-H. pylori drug that will usually be used in combination with an antibiotic. [References: 61]

Database: Medline <1966 to present>

Set	Search	Results
1	exp bismuth/	2126
2	bismuth citrate.tw.	53
3	efficacy.tw.	108250
4	safety.tw.	44957
5	exp drug therapy/	115501
6	2 and 3	11
7	2 and 4	4
8	2 and 5	13
9	from 6 keep 3-5,7-8,10	6
10	from 7 keep 3-4	2
11	from 8 keep 12-13	2
12	exp drug stability/	20813
13	2 and 12	0
14	stability.tw.	54760
15	2 and 14	0

<1>
Unique Identifier
96228244
Authors
Hunt RH.
Title
Eradication of Helicobacter pylori infection. [Review] [72 refs]
Source
American Journal of Medicine. 100(5A):42S-50S; discussion 50S-51S, 1996 May 20.
Abstract
Helicobacter pylori is probably the most common bacterial infection worldwide and the accepted cause of chronic active gastritis. It has a critical role in duodenal ulcer, where the prevalence of infection is 90-95%. There is a dramatic reduction in the rate of ulcer recurrence after successful eradication of the organism to about 4% per annum compared with up to 80% when the infection persists. What is true for duodenal ulcers is also true for patients with gastric ulcer who are infected with H. pylori. The risk of recurrent ulcer complications with bleeding is virtually abolished following successful eradication of H. pylori; in contrast, the risk of rebleeding is about 33% in patients still harboring the organism. The treatment of H. pylori infection in patients with confirmed peptic ulcer on

first presentation or recurrence has been advocated by a Consensus Conference of the National Institutes of Health. The most evaluated regimens include dual therapy with a proton pump inhibitor and either amoxicillin or clarithromycin, and bismuth-based triple therapy with metronidazole and tetracycline. The use of a proton pump inhibitor-containing regimen offers the advantage of rapid symptom relief and the highest rates of duodenal ulcer healing. Moreover, combinations of a proton pump inhibitor and clarithromycin show more predictable and higher eradication rates than amoxicillin combinations. Newer triple therapies with a proton pump inhibitor plus two antibacterial agents given for 7-10 days are being increasingly described and may become the treatment of choice if initial results are confirmed. However, the optimum dosage regimen needs to be established. A new combination of ranitidine bismuth citrate and clarithromycin has also recently been shown to be effective. At this time it is reasonable to consider all patients with confirmed duodenal or gastric ulcer for eradication of H. pylori, and no patient should be considered for elective surgery without first being offered eradication therapy. [References: 72]

<2>
Unique Identifier
92248146
Authors
Dobrilla G. Piazzi L. Amplatz S. Benvenuti S. Di Fede F.
Title
Helicobacter pylori and gastric ulcer therapy: reflections and uncertainties. [Review] [32 refs]
Source
Italian Journal of Gastroenterology. 24(2):79-84, 1992 Feb.
Abstract
The relationship between Helicobacter pylori (HP) and gastric ulcer therapy is examined by analyzing both the data that suggest that eradication of HP renders the gastric mucosa less susceptible to development of gastric ulcer as well as the substantial body of evidence that does not support this contention. The results reported in clinical trials with colloidal bismuth citrate, antimicrobial agents (furazolidone), and combinations of anti-ulcer and antimicrobial agents (H2-antagonist+cefixime, H2-antagonist+metronidazole) are reviewed. Also analyzed is the relationship between HP

eradication and ulcer recurrence. Only one study is available on this aspect, and the limited evidence it provides in favour of a prophylactic effect of eradication therapy is not entirely convincing. The authors conclude that there is no reasonable case for the dogmatic assumption that eradication of HP facilitates either acute healing or long-term prophylaxis of gastric ulcer, though certain subgroups of gastric ulcer patients may benefit from eradication therapy. [References: 32]

A. INGREDIENT NAME:

CAFFEINE CITRATED

B. Chemical Name:

C. Common Name:

Citrated Caffeine, Coffeinum Citricum

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Result)*
Assay (citric acid)	48.0-52.0%	50.5%

E. Information about how the ingredient is supplied:

White Crystalline Powder, Odorless Powder having a slightly bitter, acrid taste

F. Information about recognition of the substance in foreign pharmacopeias:

Pharmacopeias. In Aust., Hung., Ind., Roum., and Span.
B.P.C.1959
U. S. Pharmacopeia/BP 1959

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Aldridge, A. Caffeine metabolism in the newborn. *Clin. Pharmacol. Ther.*, 1979;25:447.

LeGuennec, J. C. Maturational changes of caffeine concentration and disposition in infancy during maintenance therapy for apnea of prematurity: influence of gestional age, hepatic disease, and breast-feeding. *Pediatrics*, 1985;76: 834.

Aranda, J. V. Maturation of caffeine elimination in infancy. *Arch Dis Child*, 1979; 54: 946.

Brouard, C. Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnea in premature infants. *Am. J. Dis. Child*, 1985;139:698.

Eisenberg, M. G. and Kang, N. Stability of citrated caffeine solutions for injectable and enternal use. *Am. J. hosp. Pharm.*, 1984;41(11):2405-2406.

Brouard, C., Moriette, G., and Murat,I. Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnea in premature infants. *Am. J. Dis. Child.*, 1985; 139(7): 698-700.

H. Information about dosage forms used:

Solution

I. Information about strength:

20mg

J. Information about route of administration:

Oral or Intravenous

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

3-1202
#53922

CERTIFICATE OF ANALYSIS

PRODUCT: CAFFEINE, CITRATED POWDER. GRADE:PURIFIED
RELEASE #: 103025 LOT # :B61087D17 CODE:R60938,60452

		SPECIFICATIONS	RESULT
1.	DESCRIPTION	WHITE POWDER E	CONFORMS
2.	Identification	To pass test	passes test
3.	Loss on drying	5.0% max.	0.1%
4.	Residue on ignition	0.1% max.	0.025%
5.	Heavy metals	15 ppm max.	<10 ppm
6.	Readily carbonizable substances	To pass test	CONFORMS
7.	Assay (caffeine)	48.0 - 52.0%	49.5%
	Assay (citric acid)	48.0 - 52.0%	50.5% D

ATTENTION: TONY HATCHETT

Date :10/21/97 Prepared by : J.PATEL

10700 Approved by : 10/97

Our Order # 238780 Your PO # 54210

QUALITY CONTROL REPORT

CHEMICAL NAME.: CAFFEINE CITRATED (PURIFIED) _____

MANUFACTURE LOT NO.: B61087D17

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE CRYSTALLINE, ODORLESS POWDER HAVING A SLIGHTLY BITTER, ACRID TASTE. E

2) SOLUBILITY.:
SOLUBLE IN ABOUT 4 PARTS WARM WATER.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES (B) AS PER NF 10th 1955.
B) COMPLIES (C) AS PER NF 10th 1955.

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

CITY CHEMICAL -- CAFFEINE CITRATED
MATERIAL SAFETY DATA SHEET
NSN: 685000F047602
Manufacturer's CAGE: 8G949
Part No. Indicator: A
Part Number/Trade Name: CAFFEINE CITRATED

General Information

Company's Name: CITY CHEMICAL CO
Company's Street: 100 HOBOKEN AVE
Company's City: JERSEY CITY
Company's State: NJ
Company's Country: US
Company's Zip Code: 07310-5000
Company's Emerg Ph #: 201-653-6900
Company's Info Ph #: 201-653-6900
Record No. For Safety Entry: 001
Tot Safety Entries This Stk#: 001
Status: SE
Date MSDS Prepared: 20NOV95
Safety Data Review Date: 01MAY96
Preparer's Company: CITY CHEMICAL CO
Preparer's St Or P. O. Box: 100 HOBOKEN AVE
Preparer's City: JERSEY CITY
Preparer's State: NJ
Preparer's Zip Code: 07310-5000
MSDS Serial Number: BZDDY
Hazard Characteristic Code: N/

Ingredients/Identity Information

Proprietary: NO
Ingredient: CAFFEINE CITRATE, CITRIC ACID, COMPD. WITH CAFFEINE (1:1)
96-1
Ingredient Sequence Number: 01
NIOSH (RTECS) Number: EV6495400
CAS Number: 69-22-7

Physical/Chemical Characteristics

Appearance And Odor: WHITE POWDER, ODORLESS
Solubility In Water: COMPLETE

Fire and Explosion Hazard Data

Extinguishing Media: WATERSPRAY, CO2/DRY POWDER
Special Fire Fighting Proc: WEAR FULL PROTECTIVE CLOTHING & NIOSH APPROVED SCBA W/FULL FACEPIECE OPERATED IN THE PRESSURE DEMAND/OTHER POSITIVE PRESSURE MODE.
Unusual Fire And Expl Hazrds: FIRE IS POSSIBLE AT ELEVATED TEMPS/BY CONTACT W/AN IGNITION SOURCE, FINE DUST DISPERSED IN AIR IN SUFFICIENT CONCENTRATIONS IS A POTENTIAL DUST EXPLOSION.

Reactivity Data

Stability: YES
Cond To Avoid (Stability): HEAT, IGNITION SOURCE
Hazardous Decomp Products: WHEN HEATED: EMITS TOXIC OXIDES OF NITROGEN & CARBON.
Hazardous Poly Occur: NO

Health Hazard Data

LD50-LC50 Mixture: ORAL LD50(RAT): 192 MG/KG CAFFEINE
Route Of Entry - Inhalation: YES
Route Of Entry - Skin: NO
Route Of Entry - Ingestion: YES
Health Haz Acute And Chronic: INHALATION: MILD IRRITATION TO THE HARMFUL, MAY CAUSE CNS STIMULATION & GASTRIC IRRITATION. EYES: MAY CAUSE MECHANICAL IRRITATION. CAFFEINE IS EXTENSIVELY METABOLIZED BY MAN.

Carcinogenicity - NTP: NO
Carcinogenicity - IARC: NO
Carcinogenicity - OSHA: NO
Explanation Carcinogenicity: NONE
Signs/Symptoms Of Overexp: IRRITATION, WAKEFULNESS, NAUSEA, RINGING IN EARS, MILD EXCITEMENT, PALPITATIONS, CONVULSIONS.
INDUCE VOMITING IMMEDIATELY BY GIVING 2 GLASSES OF WATER & STICKING FINGER WASH AREA W/SOAP & WATER. EYES: WASH W/PLENTY OF WATER FOR 15 MINS. OBTAIN MEDICAL ATTENTION IN ALL CASES.

Precautions for Safe Handling and Use

Steps If Matl Released/Spill: REMOVE SOURCES OF IGNITION. VENTILATE AREA OF LEAK. CLEAN UP PERSONNEL MAY REQUIRE PROTECTION FROM DUST. CLEAN UP AREA THAT DOESN'T DISPERSE DUST INTO THE AIR. USE NON-SPARKING TOOLS. PICK UP FOR RECOVERY/DISPOSAL & PLACE IN A CLOSED CONTAINER.
Waste Disposal Method: RECOVERY MAY BE BURNED IN AN APPROVED INCINERATOR/ DISPOSED IN AN APPROVED WASTE FACILITY IAW/FEDERAL, STATE & LOCAL REGULATIONS.
Precautions-Handling/Storing: KEEP IN A TIGHTLY CLOSED CONTAINER. STORE IN A COOL, DRY VENTILATED AREA AWAY FROM SOURCES OF HEAT/IGNITION. PROTECT AGAINST PHYSICAL DAMAGE.
Other Precautions: CONTACT LENSES SHOULDN'T BE WORN WHEN WORKING W/THIS MATERIAL.

Control Measures

Respiratory Protection: WHERE EXPOSURE TO THE DUST IS APPARENT, A DUST/ MIST RESPIRATOR MAY BE WORN. FOR EMERGENCIES, A SCBA MAY BE NECESSARY.
Ventilation: LOCAL EXHAUST TO PREVENT DISPERSION OF THE CONTAMINANT INTO THE WORKROOM AIR.
Protective Gloves: PROTECTIVE
Eye Protection: CHEMICAL SAFETY GOGGLES
Other Protective Equipment: CLEAN BODY COVERING CLOTHING, EYE WASH FOUNTAIN & QUICK DRENCH FACILITIES.

Transportation Data

Disposal Data

Label Data

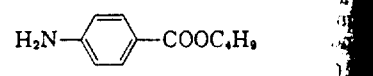
Label Required: YES
Label Status: G
Common Name: CAFFEINE CITRATED
Special Hazard Precautions: INHALATION: MILD IRRITATION TO THE RESPIRATORY TRACT & MAY BE A ROUTE OF ABSORPTION BY THE BODY. INGESTION: HARMFUL, MAY CAUSE CNS STIMULATION & GASTRIC IRRITATION. EYES: MAY CAUSE MECHANICAL IRRITATION. CAFFEINE IS EXTENSIVELY METABOLIZED BY MAN. IRRITATION, WAKEFULNESS, NAUSEA, RINGING IN EARS, MILD EXCITEMENT, PALPITATIONS, CONVULSIONS.
Label Name: CITY CHEMICAL CO
Label Street: 100 HOBOKEN AVE
Label City: JERSEY CITY
Label State: NJ
Label Zip Code: 07310-5000
Label Country: US
Label Emergency Number: 201-653-6900

per cent butethamine hydrochloride and 1 in ,000 epinephrine in 5-ml. cartridges; and in , 60-, and 125-ml. bottles; 1.5 per cent tethamine hydrochloride and 1 in 100,000 inephrine in 1-, 2-, 2.5-, and 5-ml. cartridges; 2- and 3-ml. ampuls; and in 30-, 60-, and 125- l. bottles; 1.5 per cent butethamine hydro- loride and 1 in 30,000 epinephrine in 5-ml. rtridges; 2 per cent butethamine hydro- loride and 1 in 50,000 epinephrine in 1-, 2- id 2.5-ml. cartridges; in 2- and 3-ml. ampuls id in 60- and 125-ml. bottles.

CATEGORY—See Butethamine Hydrochloride.

BUTYL AMINOBENZOATE

n-Butyl *p*-Aminobenzoate



$C_{11}H_{15}NO_2$ Mol. wt. 193.25

Description—Butyl Aminobenzoate occurs as white, crystalline powder. It is odorless and steless.

Solubility—One Gm. of Butyl Aminobenzoate ssolves in about 7000 ml. of water. It is luble in dilute acids, in alcohol, in chloroform, ether, and in fatty oils. It is slowly hydrolyzed hen boiled with water.

Identification—

A: dd a few drops of a solution of sodium itrite (1 in 10) to 2 ml. of a solution of Butyl minobenzoate in 0.1 *N* hydrochloric acid (1 in 00), and add the mixture to a solution of 20 g. of betanaphthol in 10 ml. of a solution of dium hydroxide (1 in 10): a scarlet red recipitate is produced.

B: To 1 ml. of a solution of Butyl Amino enzoate in 0.1 *N* hydrochloric acid (1 in 100 dd a few drops of iodine T.S., shake the mixture nd allow it to stand for 10 minutes with occa onal shaking: a dark brown precipitate is formed hich changes into large, reddish brown prisms nder the same conditions *ethyl aminobenzoate* ves lustrous scales).

Melting range, page 438—Butyl Amino enzoate melts between 57° and 59°.

Residue on ignition, page 448—Butyl Amino enzoate yields not more than 0.15 per cent of esidue on ignition.

Completeness and color of solution—One m. of Butyl Aminobenzoate dissolves com letely in 30 ml. of alcohol and in 30 ml. of ether nd the solutions are colorless.

Chloride—To a solution of 200 mg. of Butyl minobenzoate in 10 ml. of alcohol add 1 ml. diluted nitric acid and a few drops of silver itrate T.S.: no turbidity is produced.

Heavy metals, page 430—Dissolve 1 Gm. of utyl Aminobenzoate in 2 ml. of diluted acetic cid and sufficient alcohol to make 25 ml.; he heavy metals limit for Butyl Aminobenzoate 10 parts per million.

Packaging and storage—Preserve Butyl Aminobenzoate in well-closed containers.

CATEGORY—Local anesthetic.

BUTYL CHLORIDE

n-Butyl Chloride

$CH_3(CH_2)_2CH_2Cl$

C_4H_9Cl Mol. wt. 92.57

Butyl Chloride contains not less than 99 per cent of C_4H_9Cl.

Caution: Butyl Chloride is very flammable. Do not use where it may be ignited.

Description—Butyl Chloride occurs as a clear, colorless, volatile liquid, having a characteristic nonresidual odor. It is flammable.

Solubility—Butyl Chloride is insoluble in water, but is miscible with dehydrated alcohol and with ether.

Identification—To 20 ml. of Butyl Chloride add 5 ml. of sodium hydroxide solution (1 in 20), mix well, and boil under a reflux condenser for 1 hour: the residue responds to the tests for *Chloride*, page 433.

Specific gravity—The specific gravity of Butyl Chloride is not less than 0.880 and not more than 0.885.

Distilling range, page 413—Butyl Chloride distils between 77° and 79°.

Acidity—Transfer 35 ml. of Butyl Chloride to a separator, add 35 ml. of freshly boiled and cooled water, shake for 3 minutes, allow the mixture to separate, and collect the water layer in a suitable container. To 25 ml. of this layer add a few drops of phenolphthalein T.S. and titrate with 0.02 *N* sodium hydroxide to a pink color that persists for 30 seconds: not more than 0.1 ml. of 0.02 *N* sodium hydroxide is required for neutralization. Save the remaining 10 ml. of the water layer for use in the test for *Chloride*.

Nonvolatile residue—Evaporate 10 ml. of Butyl Chloride in a tared porcelain dish on a steam bath and dry at 105° for 1 hour: the weight of the residue does not exceed 1 mg.

Chloride, page 414—A 10-ml. portion of the aqueous layer prepared for the test for *Acidity* shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid, (7 parts per million).

Assay—Place about 1.5 ml. of Butyl Chloride in a tared, glass-stoppered flask, and weigh accurately. Add 50.0 ml. of 0.5 *N* alcoholic potassium hydroxide, and reflux on a steam bath for 30 minutes. Cool, add a few drops of phenolphthalein T.S. and titrate with 0.5 *N* hydrochloric acid. Perform a blank determination with the same quantities of the same reagents and in the same manner (see *Residual Titrations*, page 458). Each ml. of 0.5 *N* alcoholic potassium hydroxide consumed is equivalent to 46.29 mg. of C_4H_9Cl.

Packaging and storage—Preserve Butyl Chloride in well-closed, light-resistant containers, remote from fire.

CATEGORY—Anthelmintic (veterinary).

USUAL DOSE—(Based on the weight of the animal)—Horses, **15** to **90 ml.** Dogs, **1** to **24 ml.**

CITRATED CAFFEINE

Citrated Caffeine is a mixture of caffeine and citric acid containing, when dried at 80° for 4 hours, not less than 48 per cent and not more than 52 per cent of anhydrous caffeine ($C_8H_{10}N_4O_2$), and not less than 48 per cent and not more than 52 per cent of anhydrous citric acid ($C_6H_8O_7$). The sum of the percentages of anhydrous caffeine and anhydrous citric acid is not less than 98.5 and not more than 101.

Description—Citrated Caffeine occurs as a white, odorless powder, having a slightly bitter, acid taste. Its solutions are acid to litmus.

Solubility—One Gm. of Citrated Caffeine dissolves in 4 ml. of warm water. On diluting the solution with an equal volume of water, a portion of the caffeine gradually separates, but redissolves on the further addition of water.

Identification—

A: Dissolve about 20 mg. of Citrated Caffeine in 1 ml. of hydrochloric acid in a porcelain dish, add 100 mg. of potassium chlorate, and evaporate to dryness on a steam bath. Invert the dish over a vessel containing a few drops of ammonia T.S.: the residue acquires a purple color, which disappears upon the addition of a solution of a fixed alkali.

B: Dissolve about 100 mg. of Citrated Caffeine in 10 ml. of water, and add 1 ml. of calcium chloride T.S. and 3 drops of bromothymol blue T.S. Add 0.1 *N* sodium hydroxide, drop by drop, until the color of the solution just changes to a clear blue, then boil the solution gently for 3 minutes, agitating it gently during the heating period: a white, crystalline precipitate appears in the liquid.

C: Add 1 ml. of mercuric sulfate T.S. to 5 ml. of a solution of Citrated Caffeine (1 in 100), heat the mixture to boiling, and add 1 ml. of potassium permanganate T.S.: a white precipitate appears.

D: The residue obtained in the *Assay for caffeine*, when recrystallized from hot water and dried at 80° for 4 hours, melts between 235° and 237.5°, page 438.

Loss on drying, page 437—Dry Citrated Caffeine at 80° for 4 hours: it loses not more than 5 per cent of its weight.

Residue on ignition, page 448—Citrated Caffeine yields not more than 0.1 per cent of residue on ignition.

Heavy metals, page 430—Dissolve 1 Gm. of Citrated Caffeine in 15 ml. of water, and dilute to 25 ml.: the heavy metals limit for Citrated Caffeine is 15 parts per million.

Readily carbonizable substances, page 447—Heat a mixture of 250 mg. of Citrated Caffeine and 5 ml. of sulfuric acid T.S. in a porcelain dish on a steam bath for 15 minutes, protecting it from dust: the color is not darker than that of Matching Fluid K.

Assay for caffeine—Accurately weigh about 1 Gm. of Citrated Caffeine, previously dried at 80° for 4 hours, and dissolve it in 10 ml. of hot water. Add 8 ml. of sodium hydroxide T.S., cool the solution, and shake it in a separator with three or more successive portions of 20 ml. each of chloroform to effect complete extraction of the caffeine. Filter the combined chloroform solutions through a small filter, previously moistened with chloroform, into a tared dish. Wash the stem of the separator, the filter, and the funnel with 10 ml. of hot chloroform, adding the washings to the dish, and evaporate the combined chloroform solutions on a steam bath, adding 2 ml. of alcohol just before the last trace of chloroform is expelled. Complete the evaporation of the solvent, and dry the residue, consisting of $C_8H_{10}N_4O_2$, at 80° for 4 hours and weigh.

Assay for citric acid—Weigh accurately about 400 mg. of Citrated Caffeine, previously dried at 80° for 4 hours, and dissolve it in 25 ml. of water. Add 3 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to a faint pink color. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 6.404 mg. of $C_6H_8O_7$.

Packaging and storage—Preserve Citrated Caffeine in tight containers.

CATEGORY—Central stimulant.
USUAL DOSE—**300 mg.**

Citrated Caffeine Tablets

Citrated Caffeine Tablets yield an amount of anhydrous caffeine ($C_8H_{10}N_4O_2$) not less than 45 per cent and not more than 55 per cent of the labeled amount of citrated caffeine.

Identification—Citrated Caffeine Tablets respond to the *Identification tests* under *Citrated Caffeine,* page 63.

Disintegration, page 455—The disintegration time limit for Citrated Caffeine Tablets is 30 minutes.

Weight variation, page 468—Citrated Caffeine Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Citrated Caffeine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg. of citrated caffeine, to a separator, and dissolve it, as completely as possible, in 10 ml. of water. Add 1 drop of phenolphthalein T.S., and sodium hydroxide T.S. until a permanent pink color is produced. Extract the caffeine completely from the mixture with successive portions of chloroform, pass each portion through a filter which has been previously moistened with chloroform, and wash the stem of the funnel and the filter with a few ml. of hot chloroform. Evaporate the filtrate on a steam bath, adding 2 ml. of alcohol just before the chloroform is all evaporated, and dry the residue at 80° for 4 hours. The weight of residue obtained represents the yield of $C_8H_{10}N_4O_2$.

Packaging and storage—Preserve Citrated Caffeine Tablets in tight containers.

Tablets available—Citrated Caffeine Tablets usually available contain the following amounts of citrated caffeine: 60 and 120 mg.

CATEGORY and DOSE—See Citrated Caffeine.

CALAMINE OINTMENT

Turner's Cerate

Calamine	170 Gm.
Yellow Wax	40 Gm.
Wool Fat	40 Gm.
Petrolatum	750 Gm.
To make	1000 Gm.

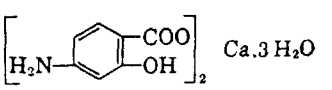
Melt the yellow wax with the wool fat and petrolatum and mix the calamine thoroughly with the melted mixture to produce a smooth, homogeneous ointment.

Packaging and storage—Preserve Calamine Ointment in tight containers and avoid prolonged exposure to temperatures above 30°.

CATEGORY—Astringent protectant.

CALCIUM AMINOSALICYLATE

Calcium Para-aminosalicylate



$C_{14}H_{12}CaN_2O_6 \cdot 3H_2O$ Mol. wt. 398.40

Calcium Aminosalicylate contains not less than 98 per cent of $C_{14}H_{12}CaN_2O_6$, calculated on the anhydrous basis.

Caution: Prepare solutions of Calcium Aminosalicylate within 24 hours of administration. Under no circumstances use a solution if its color is darker than that of a freshly prepared solution.

Description—Calcium Aminosalicylate occurs as white to cream-colored crystals or powder. It is odorless and has an alkaline, slightly bittersweet taste. It is somewhat hygroscopic. Its solutions decompose slowly and darken in color.

...feine Citrate (626-h)

...ine Citrate (BANM).

...ated Caffeine; Coffeinum Citricum.

$C_{16}H_{10}N_4O_2.C_6H_8O_7 = 386.3$.

CAS — 69-22-7.

...macopoeias. In Aust.

...eine Hydrate (622-r)

...eine Hydrate (BANM).

...eine Monohydrate; Coffeinum Monohydricum.

$C_8H_{10}N_4O_2.H_2O = 212.2$.

CAS — 5743-12-4.

Pharmacopoeias. In Aust., Belg., Br., Chin., Eur., Fr., Ger., Int., It., Jap., Neth., Port., Swiss, and US. Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

The standards of *Ph. Eur.* apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

Odourless silky white crystals, usually matted together, or a white crystalline powder. It effloresces in air and sublimes readily.

BP solubilities are: sparingly soluble in water; freely soluble in boiling water and in chloroform; slightly soluble in alcohol and in ether. It dissolves in concentrated solutions of alkali benzoates or salicylates. USP solubilities are: soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. Solutions in water are neutral to litmus. **Store** in airtight containers.

Stability. References to the stability of caffeine and caffeine citrate.

1. Eisenberg MG, Kang N. Stability of citrated caffeine solutions for injectable and enteral use. *Am J Hosp Pharm* 1984; **41:** 2405–6.
2. Nahata MC, *et al.* Stability of caffeine injection in intravenous admixtures and parenteral nutrition solutions. *DICP Ann Pharmacother* 1989; **23:** 466–7.
3. Hopkin C, *et al.* Stability study of caffeine citrate. *Br J Pharm Pract* 1990; **12:** 133.
4. Donnelly RF, Tirona RG. Stability of citrated caffeine injectable solution in glass vials. *Am J Hosp Pharm* 1994; **51:** 512–14.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p.1657.

Prolonged high intake of caffeine may lead to tolerance to some of the pharmacological actions and physical signs of withdrawal including irritability, lethargy, and headache may occur if intake is discontinued abruptly.

General references.

1. Wills S. Drugs and substance misuse: caffeine. *Pharm J* 1994; **252:** 822–4.

Effects on mental function. A report of 6 cases of excessive daytime sleepiness associated with high caffeine intake.[1]

1. Regestein QR. Pathologic sleepiness induced by caffeine. *Am J Med* 1989; **87:** 586–8.

Gastro-oesophageal reflux disease. Theophylline derivatives tend to relax the lower oesophageal sphincter and increase gastric acid secretion. For a report of increased gastro-oesophageal reflux in neonates receiving caffeine, see Gastro-oesophageal Reflux Disease under Precautions in Theophylline, p.1659.

Interactions. Caffeine is extensively metabolised primarily by microsomal enzymes in the liver. Clearance is therefore subject to interactions, in a similar manner to theophylline (see p.1659). Smoking, and drugs such as phenytoin which induce hepatic microsomal metabolism result in an increase in caffeine clearance, and drugs such as oral contraceptives reduce the rate of clearance by inhibiting caffeine metabolism. For further discussion on individual drug interactions with caffeine, see below.

ALCOHOL. In a study of 8 healthy subjects given alcohol by mouth in a dose of 2.2 mL per kg body-weight, caffeine 150 mg by mouth did not antagonise the central effects of alcohol and, instead, a synergistic interaction occurred which further increased reaction time. The common practice of drinking coffee after drinking alcohol in order to sober up is not supported by these results.[1]

1. Oborne DJ, Rogers Y. Interactions of alcohol and caffeine on human reaction time. *Aviat Space Environ Med* 1983; **54:** 528–34.

ANTIARRHYTHMICS. In 7 healthy subjects and 5 patients with cardiac arrhythmias, *mexiletine* in a single dose of 200 mg and a dose of 600 mg daily respectively, reduced the elimination of caffeine by 30 to 50%.[1] *Lignocaine*, *flecainide*, and *tocainide* had no effect on caffeine elimination in healthy subjects.[1]

1. Joeres R, Richter E. Mexiletine and caffeine elimination. *N Engl J Med* 1987; **317:** 117.

ANTIBACTERIALS. Caffeine elimination half-life has been reported to be increased and clearance decreased by the concomitant administration of *ciprofloxacin*,[1-3] *enoxacin*,[2,3] and *pipemidic acid*;[2,3] *lomefloxacin*,[4] *norfloxacin*,[2,3] and *ofloxacin*[2,3] had little or no effect on these parameters. Enoxacin had the greatest inhibitory effect on caffeine clearance.[2,3]

1. Healy DP, *et al.* Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1989; **33:** 474–8.
2. Harder S, *et al.* Ciprofloxacin-caffeine: a drug interaction established using in vivo and in vitro investigations. *Am J Med* 1989; **87** (suppl 5A): 89–91S.
3. Barnett G, *et al.* Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. *Eur J Clin Pharmacol* 1990; **39:** 63–9.
4. Healy DP, *et al.* Lack of interaction between lomefloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1991; **35:** 660–4.

ANTIEPILEPTICS. The mean clearance of caffeine was increased and its half-life decreased in epileptic patients taking *phenytoin* compared with healthy controls, resulting in lower plasma-caffeine concentrations. Treatment with *carbamazepine* or *valproic acid* had no effect on the pharmacokinetics of caffeine.[1]

1. Wietholtz H, *et al.* Effects of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. *Eur J Clin Pharmacol* 1989; **36:** 401–6.

ANTIFUNGALS. In a single-dose study in healthy subjects, *terbinafine* 500 mg by mouth decreased the clearance and increased the elimination half-life of caffeine 3 mg per kg body-weight given intravenously. *Ketoconazole* 400 mg by mouth did not prolong the elimination of caffeine to a significant extent.[1]

1. Wahlländer A, Paumgartner G. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 279–83.

ANTIGOUT AGENTS. In a study in 2 healthy subjects, the plasma half-life of caffeine was essentially unchanged by 7 days' treatment with *allopurinol* 300 mg or 600 mg daily by mouth. However, allopurinol caused a specific, dose-dependent inhibition of the conversion of 1-methylxanthine to 1-methyluric acid.[1]

1. Grant DM, *et al.* Effect of allopurinol on caffeine disposition in man. *Br J Clin Pharmacol* 1986; **21:** 454–8.

GASTRO-INTESTINAL AGENTS. *Cimetidine* 1 g daily by mouth reduced the systemic clearance of caffeine and prolonged its elimination half-life in 5 healthy subjects. Although the steady-state plasma-caffeine concentration would increase by approximately 70%, it was thought unlikely that this would produce adverse clinical effects.[1]

1. Broughton LJ, Rogers HJ. Decreased systemic clearance of caffeine due to cimetidine. *Br J Clin Pharmacol* 1981; **12:** 155–9.

IDROCILAMIDE. In 4 healthy subjects, idrocilamide inhibited the biotransformation of caffeine and increased its half-life 9 times. Partial or total avoidance of caffeine-containing products was recommended when idrocilamide was being taken.[1]

1. Brazier JL, *et al.* Inhibition by idrocilamide of the disposition of caffeine. *Eur J Clin Pharmacol* 1980; **17:** 37–43.

ORAL CONTRACEPTIVES. The clearance of caffeine has been reported to be reduced and its elimination half-life increased in women taking oral contraceptives.[1,2] This interaction was thought to be due to impairment of hepatic metabolism of caffeine by sex hormones and could result in increased accumulation of caffeine.

1. Patwardhan RV, *et al.* Impaired elimination of caffeine by oral contraceptive steroids. *J Lab Clin Med* 1980; **95:** 603–8.
2. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. *Eur J Clin Pharmacol* 1985; **28:** 425–8.

SYMPATHOMIMETICS. Administration of caffeine 400 mg with *phenylpropanolamine* 75 mg, both given orally as controlled-release preparations, produced greater plasma-caffeine concentrations in healthy subjects than administration of caffeine alone. Greater increases in blood pressure and more reports of physical side-effects occurred after the combination than after either drug alone.[1]

1. Lake CR, *et al.* Phenylpropanolamine increases plasma caffeine levels. *Clin Pharmacol Ther* 1990; **47:** 675–85.

THEOPHYLLINE. For the effect of caffeine on the metabolism and elimination of theophylline, see under Interactions in Theophylline, p.1661.

Overdosage. Reports and reviews of caffeine toxicity.

1. Kulkarni PB, Dorand RD. Caffeine toxicity in a neonate. *Pediatrics* 1979; **64:** 254–5.
2. Banner W, Czajka PA. Acute caffeine overdose in the neonate. *Am J Dis Child* 1980; **134:** 495–8.
3. Zimmerman PM, *et al.* Caffeine intoxication: a near fatality. *Ann Emerg Med* 1985; **14:** 1227–9.
4. Dalvi RR. Acute and chronic toxicity of caffeine: a review. *Vet Hum Toxicol* 1986; **28:** 144–50.

Pregnancy and the neonate. In the USA, the Food and Drug Administration has advised pregnant women to limit their intake of caffeine and caffeine-containing beverages to a minimum, but this recommendation was based largely on animal studies and the effect of caffeine on the human foetus and foetal loss during pregnancy is controversial.[1] Although one recent study found no evidence that moderate caffeine use (less than 300 mg daily) increased the risk of spontaneous abortion,[2] another study has reported conflicting results[3] leading one commentator to conclude that the safety of caffeine consumption during pregnancy remains unresolved.[1]

1. Eskenazi B. Caffeine during pregnancy: grounds for concern? *JAMA* 1993; **270:** 2973–4.
2. Mills JL, *et al.* Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *JAMA* 1993; **269:** 593–7.
3. Infante-Rivard C, *et al.* Fetal loss associated with caffeine intake before and during pregnancy. *JAMA* 1993; **270:** 2940–3.

For a comment on the inadvisability of using caffeine and sodium benzoate injection in neonates because of the risk of adverse effects associated with the benzoate component, see under Sodium Benzoate, p.1118.

LACTATION. For studies examining the transfer of caffeine into breast milk and its consequences, see p.1653 under Pharmacokinetics.

Sport. The International Olympic Committee has banned the use of large amounts of caffeine by athletes but smaller amounts, compatible with a moderate intake of coffee or soft drinks, are permitted.[1] However, because of the marked inter-individual variation in urine-caffeine concentrations, even a modest caffeine intake equivalent to 3 to 6 cups of coffee daily, may give a urine concentration in excess of the permissible limit.[2]

1. Anonymous. Drugs in the Olympics. *Med Lett Drugs Ther* 1984; **26:** 65–6.
2. Birkett DJ, Miners JO. Caffeine renal clearance and urine caffeine concentrations during steady state dosing: implications for monitoring caffeine intake during sports events. *Br J Clin Pharmacol* 1991; **31:** 405–8.

Withdrawal. Headache is a recognised symptom of caffeine withdrawal and even subjects who drink moderate amounts of coffee can develop headaches lasting 1 to 6 days when switched to a decaffeinated brand.[1] It has also been suggested that postoperative headache could be attributed to caffeine withdrawal as fasting patients are required to abstain from drinking tea or coffee before surgical procedures. Several studies[2-4] have found a positive association between postoperative headache and daily caffeine consumption, although there have also been negative findings.[5]

1. van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. *Br Med J* 1990; **300:** 1558–9.
2. Galletly DC, *et al.* Does caffeine withdrawal contribute to postanaesthetic morbidity? *Lancet* 1989; **i:** 1335.
3. Weber JG, *et al.* Perioperative ingestion of caffeine and postoperative headache. *Mayo Clin Proc* 1993; **68:** 842–5.
4. Nikolajsen L, *et al.* Effect of previous frequency of headache, duration of fasting and caffeine abstinence on perioperative headache. *Br J Anaesth* 1994; **72:** 295–7.
5. Verhoeff FH, Millar JM. Does caffeine contribute to postoperative morbidity? *Lancet* 1990; **336:** 632.

Pharmacokinetics

Caffeine is absorbed readily after oral administration and is widely distributed throughout the body. It is also absorbed through the skin. Absorption following rectal administration by suppository may be slow and erratic. Absorption following intramuscular injection may be slower than after oral administration. Caffeine passes readily into the central nervous system and into saliva; low concentrations are also present in breast milk. Caffeine crosses the placenta.

In adults, caffeine is metabolised almost completely in the liver via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged. Neonates have a greatly reduced capacity to metabolise caffeine and it is largely excreted unchanged in the urine until hepatic metabolism becomes significantly developed, usually by about 6 months of age. Elimination half-lives are approximately 3 to 6 hours in adults but may be in excess of 100 hours in neonates.

Lactation. Studies examining the transfer of caffeine into breast milk after doses of 35 to 336 mg of caffeine by mouth have recorded peak maternal plasma concentrations of 2.4 to 4.7 µg per mL, peak maternal saliva concentrations of 1.2 to 9.2 µg per mL, and peak breast-milk concentrations of 1.4 to 7.2 µg per mL. At these concentrations in breast milk, the calculated daily caffeine ingestion by breast-fed infants ranged from 1.3 to 3.1 mg, which was not thought to present a haz-

the urine as 1-methyluric acid, 1-met- , and other metabolites with only unchanged.

caffeine in man. The average plasma half- was 3.5 hours.— J. Axelrod and J. Rei- *J. Pharmac. exp. Ther.*, 1953, *107*, 519.

concentrations of 1.5 to 1.8 μg per ml were subjects 50 to 75 minutes after a dose of caffeine had been given as coffee.— F. L. J. A. Reinstein, *J. pharm. Sci.*, 1968, *57*,

and the neonate. Following the intravenous ion of caffeine to 7 infants of 2½ weeks to 6 plasma clearance progressively increased to city by 3 to 4½ months and exceeded it by 5 ths of age.— J. V. Aranda *et al.*, *Archs Dis.* 1979, *54*, 946. Further references: A. Aldridge *Clin. Pharmac. Ther.*, 1979, *25*, 447 (caffeine in neonates); J. V. Aranda *et al.*, *J. Pediat.*, 663 (pharmacokinetics in premature infants); ani *et al.*, *J. Pediat.*, 1980, *96*, 1091 (serum concentrations in premature infants).

An hour after taking 150 mg of caffeine as and sodium benzoate, peak concentrations of in 5 healthy mothers ranged from 2.39 to per ml in serum and from 1.4 to 2.4 μg per ml milk.— E. E. Tyrala and W. E. Dodson, *Archs* ., 1979, *54*, 787.

Caffeine acts on the central nervous on muscle, including cardiac muscle, and kidneys. Its action on the central nervous is mainly on the higher centres and it s a condition of wakefulness and d mental activity. Caffeine facilitates the ance of muscular work and increases the ork which can be performed by a muscle. stimulate the respiratory centre, increas- rate and depth of respiration. Its stimu- ion on the medullary vasomotor centre is compensated by its peripheral vasodilator on the arterioles, so that the blood pressure remains unchanged.

diuretic action of caffeine has been ted for in many ways. It may increase blood flow and glomerular filtration rate, main action may be due to the reduction normal tubular reabsorption. It is less e as a diuretic than theobromine which s central stimulating effect and does not insomnia. The xanthines are rarely of great in promoting increased renal function when depressed.

e is claimed to enhance the action of mine and is frequently given with ergotam- in the treatment of migraine.

ne is administered in powder or tablets in of 100 to 300 mg. It is frequently included lgesic preparations with aspirin or codeine. ges of coffee, tea, and cola provide active of caffeine.

s of the actions of caffeine.— I. B. Syed, *J. Am. Ass.*, 1976, *NS16*, 568; *Nutr. Rev.*, 1979, *37*,

hyperglycaemia occurred 2 hours after a dose of g of caffeine; the effect was rather more evident s with fewer general symptoms and signs sug- of disease.— E. Cheraskin and W. M. Ringsdorf *Lancet*, 1968, *2*, 689. See also E. Cheraskin *et* , 1967, *1*, 1299. Caffeine caused a decrease in ar concentrations in healthy individuals and an in patients with maturity-onset diabetes.— H. g *et al.*, *J. Am. med. Ass.*, 1969, *208*, 1482.

was growing evidence that caffeine and theophyl- cted by increasing the formation of catecholamines dopa in the brain.— B. Waldeck (letter), *J. Pharmac.*, 1972, *24*, 654.

was reported to be a strong prostaglandin and weak agonist.— M. S. Manku and D. F. *Lancet*, 1976, *2*, 1115.

t on the use of caffeine in cocaine substitutes Cocafine Snuff and Coca Snow Incense.— R. (letter), *New Engl. J. Med.*, 1980, *302*, 817.

Caffeine citrate was given to 17 premature with apnoea. The regimen evolved during the was a loading dose of 20 mg per kg body-weight ously followed 2 to 3 days later by maintenance of 5 to 10 mg per kg given once or twice daily. requency of apnoeic episodes was significantly reduced with complete abolition of apnoea in 6 infants. Plasma half-lives were very prolonged and ranged from 40.7 to 231.0 hours. Controlled trials were necessary to establish the usefulness of caffeine.— J. V. Aranda *et al.*, *J. Pediat.*, 1977, *90*, 467. See also *J. Am. med. Ass.*, 1976, *235*, 693; T. R. Gunn *et al.*, *J. Pediat.*, 1979, *94*, 106.

Dermatitis. In a double-blind study in 28 patients with atopic dermatitis the application for 3 weeks of a 30% caffeine cream produced significantly greater benefit (in terms of erythema, scaling, lichenification, oozing, and excoriation) than a placebo. It was considered that caffeine increased the concentrations of cyclic AMP in the skin.— R. J. Kaplan *et al.* (letter), *Archs Derm.*, 1977, *113*, 107. See also *idem*, 1978, *114*, 60.

Hyperkinetic states. Caffeine might be a suitable alternative to central nervous system stimulants for children with hyperkinetic states.— R. C. Schnackenberg, *Am. J. Psychiat.*, 1973, *130*, 796. See also C. C. Reichard and S. T. Elder, *Am. J. Psychiat.*, 1977, *134*, 144. A contrary view.— C. L. Saccar, *Am. J. Hosp. Pharm.*, 1978, *35*, 544.

Proprietary Names
No Doz *(Bristol, USA)*.

623-f

Caffeine and Sodium Benzoate *(B.P.C. 1954)*. Caffein. et Sod. Benz.; Coffeinum et Natrii Benzoas; Coffeinum-natrium Benzoicum.

CAS — 8000-95-1.

Pharmacopoeias. In *Aust., Cz., Ger., Hung., Int., It., Jap., Jug., Mex., Nord., Pol., Roum., Rus., Swiss*, and *Turk*. The specified caffeine content varies from 38 to 52%.

A mixture of caffeine and sodium benzoate containing 47 to 50% of anhydrous caffeine. It is a white odourless powder with a slightly bitter taste. **Soluble** 1 in about 1.2 of water and 1 in 30 of alcohol; slightly soluble in chloroform. A solution in water has a pH of 6.5 to 8.5. A 3.92% solution in water is iso-osmotic with serum. Solutions are **sterilised** by autoclaving or by filtration. **Incompatible** with mineral acids, iron salts, iodine, salts of heavy metals, and tannin. **Store** in airtight containers. Protect from light.

Because of its ready solubility in water caffeine and sodium benzoate has been employed for administration of caffeine by injection. A 25% solution has been used subcutaneously as a cardiac and respiratory stimulant and as a diuretic in doses of 120 to 300 mg.

Kernicterus. Sodium benzoate in caffeine and sodium benzoate injection could uncouple bilirubin from its albumin binding sites, which might induce kernicterus. Such injections should be administered with caution, if at all, to neonates with raised bilirubin concentrations.— D. Schiff *et al.*, *Pediatrics*, 1971, *48*, 139.

Preparations

Caffeine and Sodium Benzoate Injection *(U.S.P.)*. A sterile solution in Water for Injections; pH 6.5 to 8.5.

A preparation containing caffeine and sodium benzoate was formerly marketed in Great Britain under the proprietary name Elixir Sibec (*Vestric*).

624-d

Caffeine and Sodium Iodide *(B.P.C. 1968)*. Caffein. and Sod. Iod.; Iodocaffeine.

A mixture of caffeine and sodium iodide containing 47 to 50% of anhydrous caffeine. It is a white odourless powder with a bitter saline taste. **Soluble** 1 in 5 of water; partly soluble in alcohol. **Incompatible** with mineral acids, salts of heavy metals, and tannin. **Store** in airtight containers.

Caffeine and sodium iodide has the toxic effects of caffeine (p.340) and of iodine (p.862). It has been used as a cardiac and respiratory stimulant and as a diuretic. It is used for the relief of asthma. Doses of 120 to 600 mg have been given.

Preparations

Caffeine Iodide Elixir *(B.P.C. 1973)*. Caffeine 150 mg, sodium iodide 450 mg, liquorice liquid extract 0.3 ml, chloroform 0.01 ml, decoction prepared from a sufficient quantity of recently ground roasted coffee of commerce and water to 5 ml. *Dose*. 5 ml.

Eupinal *(Cuxson, Gerrard, UK)*. Contains in each 5 ml caffeine 115 mg and ammonium iodide 345 mg in infusion of coffee.

Eupnine Vernade *(Wilcox, UK)*. A solution containing in each 5 ml anhydrous caffeine 155 mg, ammonium iodide 366 mg, liquorice liquid extract 0.0175 ml, cherry-laurel aqueous extract (equivalent to hydrocyanic acid 27 μg) 0.027 ml. *Dose*. 5 ml in water once or twice daily before meals.

625-n

Caffeine and Sodium Salicylate *(B.P.C. 1949)*. Caffein. et Sod. Salicyl.; Coffeinum et Natrii Salicylas; Coffeinum-natrium Salicylicum.

CAS — 8002-85-5.

Pharmacopoeias. In *Aust.* (48 to 52%), *Ger.* (39 to 42%), *Int.* (44 to 46%), *Swiss* (46.8 to 48.6%), and *Turk.* (44 to 46%).

A mixture of caffeine and sodium salicylate containing 47 to 50% of anhydrous caffeine.
A white odourless amorphous powder or granular mass with a bitter saline taste. **Soluble** 1 in 2 of water and 1 in 25 of alcohol. A 5.77% solution in water is iso-osmotic with serum. Solutions are **sterilised** by autoclaving or by filtration. **Incompatible** with mineral acids, iron salts, iodine, salts of heavy metals, and tannin. **Store** in airtight containers. Protect from light.

Caffeine and sodium salicylate was formerly used, by subcutaneous injection as a 50% solution, as a cardiac and respiratory stimulant and as a diuretic.

626-h

Caffeine Citrate *(B.P.C. 1959)*. Caffein. Cit.; Citrated Caffeine; Coffeinum Citricum.
$C_8H_{10}N_4O_2,C_6H_8O_7 = 386.3$.

CAS — 69-22-7.

Pharmacopoeias. In *Aust., Hung., Ind., Roum.*, and *Span.*

A mixture of caffeine and citric acid containing 47 to 50% of anhydrous caffeine.
A white odourless powder with a bitter acid taste. **Soluble** 1 in 4 of hot water, dissociating on further dilution with the separation of caffeine on cooling which redissolves in about 32 of water; soluble 1 in 25 of alcohol. A solution in water is acid to litmus. **Incompatible** with mixtures containing potassium iodide and nitrous ether spirit, iodine being liberated. Incompatible with phenazone, sodium benzoate, sodium nitrite, and sodium salicylate; caffeine, in half the dose of caffeine citrate ordered, should be used for mixtures containing these incompatible substances. **Store** in airtight containers.

Caffeine citrate has been used similarly to caffeine (p.341) in doses of 120 to 600 mg.

627-m

Acepifylline. Acefylline Piperazine; Piperazine Theophylline Ethanoate. Piperazine bis(theophyllin-7-ylacetate).
$(C_9H_{10}N_4O_4)_2,C_4H_{10}N_2 = 562.5$.

CAS — 18833-13-1.

A white odourless crystalline powder with a bitter taste. M.p. 260°. Freely **soluble** in water; slightly soluble in alcohol. A 10% solution in water has a pH of about 7.

Adverse Effects, Treatment, and Precautions. As for Aminophylline, p.342. Acepifylline is considered to cause less nausea and gastric irritation than aminophylline and is better tolerated by intramuscular injection.

Uses. Acepifylline is a theophylline derivative which is used similarly to aminophylline (see p.344).
It may be given by mouth in doses of 0.5 to 1 g thrice daily, by rectum as suppositories in doses

THE CLINICAL USE OF DRUGS

LLOYD YEE YOUNG
MARY ANNE KODA-KIMBLE

34. S.M. was given aminophylline 6 mg (6 mg/kg of aminophylline, 4.8 mg/kg theophylline) as an IV loading dose over 20 min. Maintenance doses of 1 mg Q 8 hr have been ordered. Describe your pharmacotherapeutic monitoring plan for S.M. Include monitoring parameters for efficacy and toxicity and duration of therapy.

The goal of methylxanthine therapy in the treatment of apnea of prematurity is to decrease the number of episodes of apnea and bradycardia. Continuous monitoring of heart rate and respiratory rate is required for proper evaluation. The time, duration, and severity of episodes; activity of the infant; and any necessary intervention performed should be documented. Relationships between the apneic episodes and the feeding schedule and volume of feeds, as well as the dosing schedule of theophylline (e.g., trough), should be examined.

Apnea of prematurity usually resolves after 36 weeks postconceptional age; however, it may persist in some infants up to or beyond 40 weeks postconceptional age.[136] Therefore, methylxanthine therapy usually is discontinued at 35 to 37 weeks postconceptional age provided that the infant has not been having apneic spells.[141] Infants that require therapy for longer periods of time may be discharged home on methylxanthines with apnea monitors.

Toxicities noted in neonates include tachycardia, agitation, irritability, hyperglycemia, feeding intolerance, gastroesophageal reflux, and emesis or occasional spitting up of food. Tachycardia is the most common toxicity and usually responds to a downward adjustment of the theophylline dose. Tachycardia may persist for one to three days after dosage reductions due to the decreased elimination of theophylline-derived caffeine. Seizures also have been reported with accidental overdoses. Methylxanthine toxicity can be minimized with careful dosing and appropriate monitoring of serum concentrations. Serum theophylline concentrations should be monitored 72 hours after initiation of therapy or after a change in dosage. Serum concentrations of theophylline also should be measured if the infant experiences an increase in the number of apneic episodes, signs or symptoms of toxicity, or a significant increase in weight. In asymptomatic neonates, once steady-state levels are obtained, theophylline concentrations may be monitored every two weeks.

35. S.M. now is 3 weeks old (32 weeks postconceptional age) and weighs 1100 gm. His septic work-up was negative. Currently S.M. has several apneic spells per day which respond to tactile stimulation; his apneic episodes have not required ventilatory assistance. S.M. receives 1 mg aminophylline IV Q 8 hr and his trough theophylline level this morning was 5.7 µg/mL. The medical team is considering switching S.M.'s theophylline therapy to caffeine because of possible improved benefits. How does caffeine compare to theophylline with regard to its pharmacokinetics, efficacy, and toxicity? What treatment should be selected?

Pharmacokinetics. The plasma clearance of caffeine is considerably lower and the half-life is extremely prolonged in the premature newborn (see Table 96.2). The low clearance is a reflection of the decreased neonatal hepatic metabolism and a resultant dependence of elimination on the slow urinary excretion. In the preterm neonate, the amount of caffeine excreted unchanged in the urine is 85%, compared to less than 2% in adults. Adult urinary metabolite patterns are seen by seven to nine months of age.[154] The half-life of caffeine decreases with increasing postconceptional age[155] and plasma clearance reaches adult levels after 3 to 4.5 months of life.[156] As a result of the maturational changes, doses usually need to be adjusted after 38 weeks postconceptional age and dosing intervals need to be shortened to eight hours after 50 weeks postconceptional age.[155]

Efficacy, Toxicity, and Dosing. Comparative studies have found similar efficacy for theophylline and caffeine in the control of apnea of prematurity.[157,158] Caffeine, however, may have some advantages over theophylline including a wider therapeutic index. Adverse effects such as tachycardia, CNS excitation, and feeding intolerance are reported more frequently with theophylline than with caffeine. The prolonged half-life of caffeine in premature neonates results in less fluctuation in plasma concentrations and permits the use of a 24-hour dosing interval. Since the half-life is prolonged and dosing requirements do not change quickly over time, caffeine serum concentrations can be monitored less frequently. Oral or IV loading doses of 10 mg/kg of caffeine base (20 mg/kg of caffeine citrate), followed by maintenance doses of 2.5 mg/kg (5 mg/kg caffeine citrate) given daily will maintain plasma caffeine concentrations in the therapeutic range (5 to 20 µg/mL).[144]

Although infants who are unresponsive to theophylline may respond to caffeine,[159] S.M.'s theophylline therapy presently is not optimized; his serum concentration is less than 6 µg/mL. S.M. appears to have partially responded to theophylline and may benefit from an increase in the dose with resultant therapeutic serum concentrations. S.M.'s aminophylline dose should be increased to 1.5 mg every eight hours to achieve serum concentrations of around 8 µg/mL. Although caffeine may have several advantages over theophylline, the IV product marketed in the U.S. is only available as the sodium benzoate salt. Benzoic acid has been associated with the gasping syndrome and also may displace bilirubin from albumin binding sites.[34,35] Because of these toxicities, caffeine sodium benzoate should not be used in neonates. It is possible, however, to compound an acceptable IV and oral caffeine preparation.[160] As for any compounded injectable preparation, quality control must be done to assure sterility, stability, and lack of pyrogen contamination. If the hospital currently is not compounding an IV caffeine product, it could take months to institute quality control measures.

Other Agents

36. S.M.'s dose of theophylline has been optimized and theophylline serum concentrations now are 12.4 µg/mL. S.M. continues to have apneic episodes. What other pharmacologic agents can be used?

Doxapram, an analeptic agent, has been shown to be as effective as theophylline for the treatment of apnea of prematurity.[161,162] Due to the limited number of investigations and uncertain side effects, however, the use of doxapram should be restricted to patients who are refractory to methylxanthine therapy.[144] In addition, the IV preparation commercially available in the U.S. contains 0.9% benzyl alcohol and should be used with caution. Although doses are not well defined, a loading dose of 2.5 to 3 mg/kg given IV over 15 to 30 minutes followed by a 1 mg/kg/hour continuous infusion has been recommended.[144,163] Doses may be increased by 0.5 mg/kg/hour increments to a maximum dose of 2.5 mg/kg/hour.[144] Lower doses have been used in infants receiving concomitant methylxanthine therapy with approximately 50% responding to IV doxapram doses of 0.5 mg/kg/hour.[164] A few studies have administered doxapram enterally; however, bioavailability in preterm newborns is not yet well defined.[144,165] Side effects associated with doxapram include: increased blood pressure (usually with doses >1.5 mg/kg/hour);[164] GI disturbances such as abdominal distension, regurgitation, increased gastric residuals, and vomiting; and CNS adverse effects such as increased agitation, excessive crying, jitteriness, irritability, disturbed sleep, and seizures. Further studies of doxapram are needed in order to better delineate its adverse effects and to help define its safety and efficacy for the treatment of apnea of prematurity.

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TITLE: **Stability of citrated caffeine solutions for injectable and enteral use.**

AUTHOR: Eisenberg MG; Kang N

SOURCE: Am J Hosp Pharm 1984 Nov;41(11):2405-6

NLM CIT. ID: 85069497

MAIN MESH SUBJECTS: Caffeine/*ADMINISTRATION & DOSAGE

ADDITIONAL MESH SUBJECTS:
Administration, Oral
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Injections
Solutions
Time Factors

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS:
0 (Solutions)
58-08-2 (Caffeine)

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TITLE: Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnea in premature infants.

AUTHOR: Brouard C; Moriette G; Murat I; Flouvat B; Pajot N; Walti H; de Gamarra E; Relier JP

SOURCE: Am J Dis Child 1985 Jul;139(7):698-700

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ABSTRACT: The purpose of our prospective randomized study was to compare the efficacy of theophylline ethylenediamine and caffeine sodium citrate in the treatment of idiopathic apnea in premature infants. Sixteen infants with three or more severe apneic attacks were studied. Twenty-four-hour cardiorespiratory recordings immediately before and after randomization and four days later showed similar significant decreases of the apnea frequency in both theophylline- (group 1, n = 8) and caffeine-treated infants (group 2, n = 8). No undesirable side effects were observed, except for tachycardia in one infant in group 1. We suggest reasons for preferring caffeine to theophylline in the control of idiopathic apnea in premature infants: caffeine is as efficient and easier to administer.

MAIN MESH SUBJECTS:
Apnea/*DRUG THERAPY
Caffeine/BLOOD/*THERAPEUTIC USE
Infant, Premature, Diseases/*DRUG THERAPY
Theophylline/ADVERSE EFFECTS/BLOOD/*THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS:
Comparative Study
Human
Infant, Newborn
Support, Non-U.S. Gov't
Tachycardia/CHEMICALLY INDUCED

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Stability of citrated caffeine solutions for injectable and enteral use

MARION G. EISENBERG AND NANCY KANG

Am J Hosp Pharm. 1984, 41:2405–6

Caffeine is used to treat apnea in premature infants because it increases central nervous system response to carbon dioxide.[1] The use of citrated caffeine for apnea of prematurity is mentioned frequently in the literature, but no formulations for injectable or oral use, nor studies of their stabilities, have been published to date. This study was undertaken to fill that gap.

Methods. A formulation developed at Montreal Children's Hospital in Montreal, Quebec, Canada, provides 10 mg active caffeine base per milliliter of solution. The procedure uses bacteriostatic water to dissolve the citrated caffeine powder. Because of recent information regarding toxicity in preterm infants of benzyl alcohol, the preservative in bacteriostatic water,[2] we used Sterile Water for Injection, USP, in our formulation.

Preparation for Injectable Use. Citrated caffeine powder (purified, Mallinckrodt, Incorporated, St. Louis, MO) 10 g was dissolved in Sterile Water for Injection, USP, 250 ml. The solution was transferred into a 500-ml empty evacuated container (EEC) using a plasma transfer set. The same EEC was filled with sterile water to the 500-ml mark. The solution was filtered through a 0.22-μm filter set into another 500-ml EEC. The solution was then transferred into sterile 10-ml empty vials.

The vials containing the injectable citrated caffeine solution were autoclaved at 121 °C for 15 minutes and allowed to cool. Each vial was labeled and sealed with an IVA seal (U.S. Clinical Products, Richardson, TX 75083). One vial was sent as a sample to the bacteriology laboratory for sterility testing. Another vial from each batch was used for stability testing at time zero and at monthly intervals for four months.

Preparation for Enteral Use. Citrated caffeine powder (purified, Mallinckrodt) 10 g was dissolved in Sterile Water for Irrigation, USP, 250 ml. The mixture was stirred until completely clear. A flavoring agent (simple syrup and cherry syrup in a 2:1 ratio) was added to increase the volume to 500 ml. Initially, 10 ml of solution from each of three batches was sent to the laboratory for assay. Samples from the three batches were taken on days 14, 30, 60, and 90, and one batch was studied at day 120.

Assay Method. The concentration of caffeine in solution was determined by high-performance liquid chromatography (HPLC) as described by Ou and Frawley.[3] This method differentiates between caffeine peaks on the chromatogram and peaks made by other methylxanthines such as theophylline and theobromine.

Dilutions of 1:500 and 1:1000 were prepared for chromatography. Each sample contained the citrated caffeine solution 0.1 ml, internal standard (α-hydroxyethyl theophylline 15 μg/ml) in acetonitrile (HPLC grade) 0.1 ml, and extraction solvent (HPLC grade 95% chloroform and HPLC grade 5% 2-propanol) 2 ml. Each sample was vortexed for 30 seconds in a 13 × 100 mm glass test tube. The tube was then centrifuged for five minutes at 3000 r.p.m., and the bottom layer was transferred to a clean test tube and evaporated to dryness. The residue was dissolved in methanol 75 μl, and 20 μl of the dissolved sample was injected for the assay. The results were calculated based upon the peak height ratio of caffeine to the internal standard. Each sample was run twice at each dilution. Stability was assumed if the reported concentration was ≥90% of the original intended concentration.

Results and Discussion. Results are in Table 1. Assuming that caffeine concentrations of ≥90% of intended concentration are stable, results indicate that both the injectable and enteral products are stable for at least 90 days. Results for the injectable batches and for one enteral batch indicate the possibility of extending usable shelf-life to 120 days. Two batches that were run in duplicate confirmed our initial results. A third enteral batch was run because of slight deviation in results for our second batch.

A concentration at time zero for injectable solution 1 was not obtained because of coordination difficulties between the laboratory and the pharmacy. No sample of enteral solution 1 was sent on day 90, and no samples for enteral solutions 2 and 3 were obtained on day 120 because of the small demand for the solution beyond the three-month period.

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Table 1.
Caffeine Concentrations[a] (mg/ml) in Injectable and Enteral Solutions

Sampling Day	Solution 1	Solution 2	Solution 3
Injectable			
0	. . .	9.9	. . .
30	10.2	9.7	. . .
60	9.9	11.0	. . .
90	10.2	9.1	. . .
120	9.2	9.6	. . .
Enteral			
0	9.5	8.6	10.8
14	10.1	9.0	10.0
30	10.4	10.0	10.0
60	9.7	9.6	11.2
90	. . .	8.7	11.4
120	10.0	. . .	. . .

[a] Concentrations reflect average value of each sample run; initial concentration was 10 mg/ml.

Tests for microbial growth were negative. Sterility testing is performed for each new lot of injectable caffeine that is compounded by the pharmacy; the product is quarantined for 14 days before use, to await final cultures.

Conclusion. Extemporaneously prepared solutions of citrated caffeine in sterile water and in syrup are stable for at least three months.

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REFLECTIONS

Pharmacist in paradise

GORDON G. MCGUIRE

Am J Hosp Pharm. 1984; 41:2406–9

One of the numerous inducements for entering the health profession is the idea that the universal need for health care allows an almost unlimited choice of places in which to practice. Unfortunately, opportunities to work in exotic settings are extremely rare and finding a position is more frequently a product of chance than of design.

This was true in my case. Practicing pharmacy on a tropical island in the Pacific was mere fantasy: The reality crept up on me. In the winter of 1979–80 while I was employed as a staff pharmacist at University of California–San Diego Medical Center, I heard about a pharmacy teaching position in Micronesia.

A Federal Health Manpower Development Grant had been funded that called for a multidisciplinary training program to be centered on Ponape in the Eastern Caroline Islands. It included a special provision from the National Health Service Corps (NHSC) to have a group of health-care professionals who could serve as on-site faculty. In all, the NHSC agreed to provide six practitioners—an internist, a pediatrician, an obstetrician-gynecologist, a surgeon, a dentist, and a pharmacist. Ultimately, all positions except the surgeon's were filled.

The program's funding allowed the practitioners to bring their families, some household goods, and a motor vehicle. My wife and 8-year-old son accepted this exotic adventure enthusiastically. My decision was finalized when the Medical Center agreed to grant me a two-year leave of absence, thus alleviating my concern about finding work when the adventure was over.

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Comparative Efficacy of Theophylline and Caffeine in the Treatment of Idiopathic Apnea in Premature Infants

Christine Brouard, MD; Guy Moriette, MD; Isabelle Murat, MD; Bernard Flouvat, PharmD; Nicole Pajot; Hervé Walti, MD; Edurne de Gamarra, MD; Jean-Pierre Relier, MD

• **The purpose of our prospective randomized study was to compare the efficacy of theophylline ethylenediamine and caffeine sodium citrate in the treatment of idiopathic apnea in premature infants. Sixteen infants with three or more severe apneic attacks were studied. Twenty-four–hour cardiorespiratory recordings immediately before and after randomization and four days later showed similar significant decreases of the apnea frequency in both theophylline- (group 1, n = 8) and caffeine-treated infants (group 2, n = 8). No undesirable side effects were observed, except for tachycardia in one infant in group 1. We suggest reasons for preferring caffeine to theophylline in the control of idiopathic apnea in premature infants: caffeine is as efficient and easier to administer.**

(*AJDC* 1985;139:696-700)

Theophylline is widely used to control apnea in premature infants.[1] Doses of theophylline must be chosen carefully, and the serum theophylline concentration must be monitored regularly to avoid theophylline toxicity.[2] This risk and the occurrence of troublesome side effects in some cases[2] make the use of theophylline rather problematical.

We have previously confirmed that caffeine is also effective in controlling apnea.[3]

The present study was designed to compare the efficacy of both theophylline and caffeine in the treatment of recurrent idiopathic apnea in premature infants.

From the Service de Médecine Néonatale (Drs Brouard, Moriette, Murat, Walti, de Gamarra, and Relier and Ms Pajot) and Centre de Recherches de Biologie du Développement Foetal et Néonatal (Drs Brouard, Moriette, Murat, Walti, de Gamarra, and Relier and Ms Pajot), Hôpital Port-Royal and the Laboratoire de Toxicologie, Hôpital Ambroise Paré (Dr Flouvat), Paris.

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PATIENTS AND METHODS

Patient Selection

Apneic spells in premature infants treated in our neonatal intensive care unit (Port-Royal Hospital, Paris) were detected during routine cardiorespiratory monitoring. In those infants with apnea, 24-hour cardiorespiratory recordings (Hewlett Packard model 78250 A) enabled us to identify severe apneic attacks, defined as cessation of breathing for more than 10 s, with heart rate below 80 beats per minute for more than 30 s or below 60 beats per minute for more than 15 s.[3]

Infants with three or more severe apneic attacks within this first recording period, which was called "day 0," were considered for entry to the trial. Infants with a known cause of apnea and/or abnormal conditions other than apnea, however, were carefully excluded before randomization. Thus, the following abnormalities were ruled out: respiratory distress and/or hypoxemia; patent ductus arteriosus; anemia; metabolic abnormalities (blood glucose concentration, <40 mg/dL; plasma calcium level, <8 mg/dL; plasma bilirubin level, >10 mg/dL); infection; neurological and electroencephalographic abnormalities; and intracranial hemorrhage (using ultrasounds). Infants requiring oxygen were not included in this study.

During the 24-month period of the study, 16 preterm infants met these criteria and were admitted to the study after parental consent had been obtained.

Procedure

Infants entering the trial were randomly assigned to the theophylline-treated (group 1) or the caffeine-treated (group 2) group. The corresponding treatment was started immediately after randomization.

In group 1, a loading dose of 5.5 mg/kg of aminophylline (theophylline ethylenediamine) was injected intravenously. Fo measurements of plasma concentrations theophylline during the next eight hou enabled evaluation in each case of t proper maintenance dose, which was giv every eight hours either intravenously orally. Maintenance doses (range, 0.8 to 2 mg/kg every eight hours) were adjust thereafter according to plasma levels theophylline, which we aimed to mainta between 5 to 10 mg/L.

In group 2, a loading dose of caffei sodium citrate (20 mg/kg) was injected i tramuscularly (0.8 mL/kg, outer part of t thigh). The daily maintenance dose 5 mg/kg, which was given orally, was aim to maintain the caffeine plasma level b tween 8 and 16 mg/L. Plasma levels caffeine were measured 24 hours after t loading dose and four days later.

Plasma theophylline and caffeine conce trations were determined by high-perfor ance liquid chromatography on 100 μL plasma.[4]

For theophylline levels of 5 and 15 mg/l the "interday" coefficients of variation we 4.2% (n = 30) and 3.36% (n = 25), respe tively.

For caffeine levels of 5 and 15 mg/L, t corresponding values were 4.7% (n = 3 and 4.1% (n = 25), respectively.

We compared the efficacy of both dru using cardiorespirographic recording which were performed during the 24 hou following the loading dose ("day 1") a again four days later ("day 5").

In each 24-hour recording period (days 1, and 5), we calculated the "apnea fr quency" defined as the average number severe apneic attacks per 100 minutes. T apnea frequencies on days 0, 1, and 5 we compared for both groups using differe methods: (1) three-way analysis of varian for apnea frequencies and day, taking in account the subject factor nested in da and (2) the *t* test with the residual varian for differences in apnea frequencies b tween days 0 and 1 and between days 0 a 5. Results were expressed as mean ± SE

We looked for possible adverse effects

...nea Frequency in Theophylline- and Caffeine-Treated Infants*

Day	Group, Mean ± SEM: Theophylline	Caffeine	P
0	1.02 ± 0.4	1.42 ± 0.7	NS
1	0.12 ± 0.04†	0.13 ± 0.1†	NS
5	0.06 ± 0.02‡	0.07 ± 0.02‡	NS

*Apnea frequency (number of severe apneas per 100 minutes) in theophylline- and caffeine-treated infants. NS indicates not significant.
†$P<.001$ (days 0 to 1).
‡$P<.001$ (days 0 to 5).

the treatments by repeated clinical examination and by following weight curves.

RESULTS

Group Comparisons

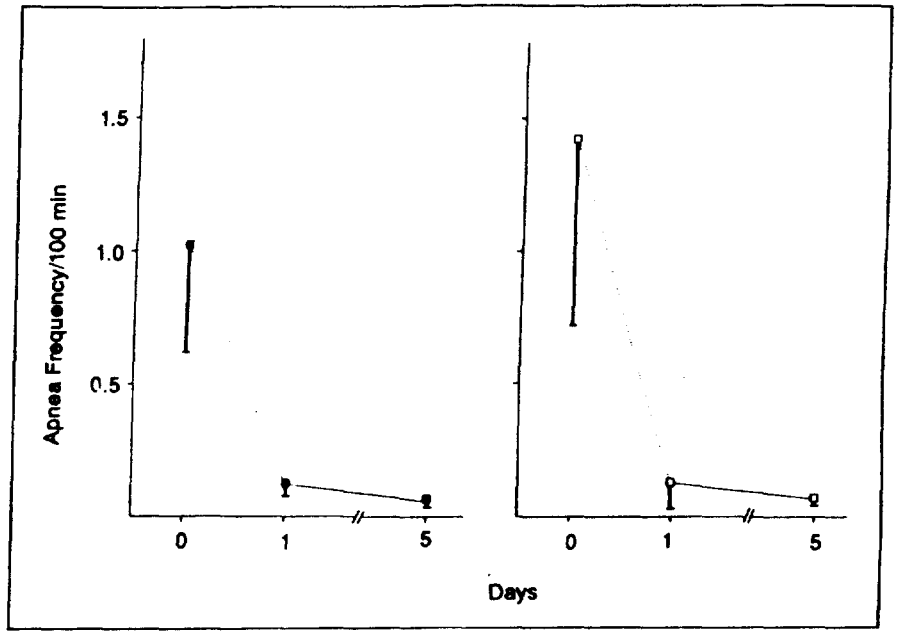
Sixteen infants were admitted to the study. Eight were treated with theophylline (group 1) and eight were treated with caffeine (group 2). There was no significant difference between the two groups for gestational age (group 1, 30.5 ± 0.4 weeks; group 2, 30.5 ± 0.7 weeks), birth weight (group 1, 1.250 ± 0.074 kg; group 2, ± 0.101 kg), postnatal age at trial (group 1, 11.7 ± 1.9 days; group 2, 11.6 ± 2.8 days), or apnea frequency on day 0 (group 1, 1.02 ± 0.4; group 2, 1.42 ± 0.7) (Table).

As compared to day 0, the 24-hour recordings on days 1 and 5 showed significant decreases of the apnea frequency in both theophylline-treated (group 1) and caffeine-treated infants (group 2) ($P<.001$) (Figure).

There were no significant differences in the frequency of apnea between the two groups, on days 0, 1, and 5.

In group 1, the mean plasma level of theophylline was 4.99 ± 0.36 mg/L on day 1 (four hours following the loading dose). Using different maintenance doses (range, 0.8 to 2.5 mg/kg every eight hours), the mean plasma level on day 5 was 6.50 ± 0.29 mg/L. We looked for transformation of theophylline into caffeine in five infants of this group,[6] and found caffeine plasma levels from 0.97 to 4.10 mg/L with theophylline levels from 3.06 to 21.2 mg/L (20 blood samples).

In group 2, the mean plasma levels of caffeine were 12.85 ± 1.32 mg/L on day 1 (4 hours after the loading dose). Using the standard maintenance dose of caffeine (5 mg/kg), the mean plasma level on day 5 was 12.74 ± 0.29 mg/L.



Evolution of apnea frequency (number of severe apneas per 100 minutes) in theophylline-treated (at left) and caffeine-treated (at right) infants. Apnea frequency decreases from days 0 to 1 ($P<.001$) and from days 0 to 5 ($P<.001$) in both groups.

Adverse Effects

No adverse effects were observed before day 5 in either group. After completion of the study, tachycardia (heart rate between 165 and 210 beats per minute) was observed during 24 hours in one theophylline-treated infant on day 6. The maintenance dose that had been given to this infant was 0.9 mg/kg every eight hours. The corresponding theophylline plasma level was 21.6 mg/L.

No adverse effect was observed in caffeine-treated infants.

COMMENT

We designed the present study to compare the efficacy of theophylline and caffeine in the treatment of recurrent idiopathic apnea in premature infants.

Our previously controlled study[4] had shown that caffeine decreases significantly the incidence of idiopathic apnea in premature infants. This efficacy had been demonstrated for both severe apneic attacks (as defined in the present study) and for milder forms of apnea. In contrast with the treated group, the apnea frequency did not change from days 0 to 1 and from days 0 to 5 in the control group. Moreover, in six of nine infants in this control group, a treatment had to be started because of recurrence of severe apneic attacks: the first two infants had to be intubated, and caffeine was used in the four others (effects of this treatment in such "control" babies were not included in the study).[3]

We had established, thus, that the spontaneous course of severe apneic attacks usually was not favorable, and that caffeine was able to change it. When we designed the present study, therefore, we found it unethical to include a control group. This present study confirms the efficacy of both theophylline and caffeine in the treatment of the most severe forms of apneic attacks. We did not assess the efficacy of either treatment on milder forms of apnea, the frequency of which is likely to decrease with both drugs, as it does with caffeine.[3]

In comparing the efficacy of these two xanthines on severe apneic attacks, we could not demonstrate any difference between the two xanthines. Thus, similar decreases of apnea frequencies were observed in both groups from days 0 to 1 and from days 0 to 5, and no significant difference could be

shown between the two groups when apnea indexes on days 0, 1, and 5 were compared.

Both theophylline and caffeine proved to be safe, as demonstrated by the absence of any complication or severe adverse effect. We observed no signs of excessive central nervous system stimulation, such as jitteriness or seizures, no abdominal distention or related problem, and no influence of the treatment on the weight curve.

It was less easy, however, to use theophylline than caffeine. The half-life of theophylline was shorter (mean, 19.5 ± 3 hours; range, 16 to 25 hours in our infants) than that of caffeine (66.1 ± 10.7 hours).[3] We chose therefore to give theophylline three times a day, as opposed to once a day for caffeine. Using the same doses, plasma levels of theophylline were variable. This is a potential risk because therapeutic and toxic levels are close. Using theophylline, plasma levels of both theophylline and caffeine, therefore, have to be repeatedly measured to allow for dosage adjustments.

Despite these adjustments, however, the plasma theophylline level was too high (21.3 mg/L) in one infant who had tachycardia.

Since we completed our first study,[3] we have been using caffeine routinely to treat apnea. In this experience, as well as in the present study, the intramuscular route has been used to inject the loading dose. It did not induce any local reaction, despite the acidity of caffeine, perhaps because the volume injected is very small. We never observed any severe adverse effect of caffeine, the toxicity of which appears very low. The ease of obtaining steady plasma levels when us caffeine once a day is in contrast w the difficulties of using theophylli Because dosage adjustment is rar required and the risk appears minim we think that, following the first f days of treatment, the plasma caffei level does not have to be measur more often than one to two times week.

In conclusion, we suggest that c feine, which is no less efficient th theophylline and is easier to us might be the drug of choice for initi treatment of apnea in premature i fants.

This study was supported by the Unité d'E seignement et de Recherche René Descartes.

We gratefully acknowledge the assistance Claude Gaudebout (INSERM U. 13) for stat tical analysis. We thank Françoise Morel-Ka and the secretaries for their help.

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Book Review

Topics in Neonatal Neurology, edited by Harvey B. Sarnat, 299 pp, with illus, New York, Grune & Stratton Inc, 1984.

This text was conceived as a selection of topics in neonatal neurology in which there have been recent rapid advances in knowledge. Several topics are discussed by more than one contributor. The book appears to be targeted mainly toward neurologists involved in the care of newborns, although neonatologists will certainly appreciate many of the topics.

The varieties of neonatal seizures are described under three topics: the diagnosis and management of hypoxia-ischemia, the electroencephalogram (EEG) in the neonatal period, and neonatal seizures. In the latter, the important role of the EEG in the identification of subtle seizures is stressed, and it is emphasized that stereotyped movements and generalized parasympathetic discharges are common release phenomena and rarely represent true seizures, as reflected by EEG ictal activity.

Perinatal cerebral hypoxia-ischemia is discussed as two topics. The section on pathogenesis and neuropathology focuses on traditional pathologic concepts and on more recent ideas of abnormal cerebral blood flow and perfusion. Current concepts of the causes of periventricular and intraventricular hemorrhage—in particular, alterations cerebral blood flow and capillary injury—are outlined another section.

Neonatal bilirubin encephalopathy and hyperammon mic encephalopathies are discussed as separate topics, a there is a section on the neurologic complications of me ingitis.

The pathophysiology of idiopathic apnea of prematurity reviewed with emphasis on rapid eye movement physiolog although, as correctly stated in a subsequent section, t rapid eye movement state is not fully developed in the ve premature infant. A discussion of ultrasound in the dia nosis of developmental defects and cerebral ischemic lesio would have been useful.

I recommend this book to anyone concerned with t neurological care of the newborn as a sound update recent advances in this rapidly changing area.

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Stability of citrated caffeine solutions for injectable and enteral use

MARION G. EISENBERG AND NANCY KANG

Am J Hosp Pharm. 1984, 41:2405–6

Caffeine is used to treat apnea in premature infants because it increases central nervous system response to carbon dioxide.[1] The use of citrated caffeine for apnea of prematurity is mentioned frequently in the literature, but no formulations for injectable or oral use, nor studies of their stabilities, have been published to date. This study was undertaken to fill that gap.

Methods. A formulation developed at Montreal Children's Hospital in Montreal, Quebec, Canada, provides 10 mg active caffeine base per milliliter of solution. The procedure uses bacteriostatic water to dissolve the citrated caffeine powder. Because of recent information regarding toxicity in preterm infants of benzyl alcohol, the preservative in bacteriostatic water,[2] we used Sterile Water for Injection, USP, in our formulation.

Preparation for Injectable Use. Citrated caffeine powder (purified, Mallinckrodt, Incorporated, St. Louis, MO) 10 g was dissolved in Sterile Water for Injection, USP, 250 ml. The solution was transferred into a 500-ml empty evacuated container (EEC) using a plasma transfer set. The same EEC was filled with sterile water to the 500-ml mark. The solution was filtered through a 0.22-μm filter set into another 500-ml EEC. The solution was then transferred into sterile 10-ml empty vials.

The vials containing the injectable citrated caffeine solution were autoclaved at 121 °C for 15 minutes and allowed to cool. Each vial was labeled and sealed with an IVA seal (U.S. Clinical Products, Richardson, TX 75083). One vial was sent as a sample to the bacteriology laboratory for sterility testing. Another vial from each batch was used for stability testing at time zero and at monthly intervals for four months.

Preparation for Enteral Use. Citrated caffeine powder (purified, Mallinckrodt) 10 g was dissolved in Sterile Water for Irrigation, USP, 250 ml. The mixture was stirred until completely clear. A flavoring agent (simple syrup and cherry syrup in a 2:1 ratio) was added to increase the volume to 500 ml. Initially, 10 ml of solution from each of three batches was sent to the laboratory for assay. Samples from the three batches were taken on days 14, 30, 60, and 90, and one batch was studied at day 120.

Assay Method. The concentration of caffeine in solution was determined by high-performance liquid chromatography (HPLC) as described by Ou and Frawley.[3] This method differentiates between caffeine peaks on the chromatogram and peaks made by other methylxanthines such as theophylline and theobromine.

Dilutions of 1:500 and 1:1000 were prepared for chromatography. Each sample contained the citrated caffeine solution 0.1 ml, internal standard (α-hydroxyethyl theophylline 15 μg/ml) in acetonitrile (HPLC grade) 0.1 ml, and extraction solvent (HPLC grade 95% chloroform and HPLC grade 5% 2-propanol) 2 ml. Each sample was vortexed for 30 seconds in a 13 × 100 mm glass test tube. The tube was then centrifuged for five minutes at 3000 r.p.m., and the bottom layer was transferred to a clean test tube and evaporated to dryness. The residue was dissolved in methanol 75 μl, and 20 μl of the dissolved sample was injected for the assay. The results were calculated based upon the peak height ratio of caffeine to the internal standard. Each sample was run twice at each dilution. Stability was assumed if the reported concentration was ≥90% of the original intended concentration.

Results and Discussion. Results are in Table 1. Assuming that caffeine concentrations of ≥90% of intended concentration are stable, results indicate that both the injectable and enteral products are stable for at least 90 days. Results for the injectable batches and for one enteral batch indicate the possibility of extending usable shelf-life to 120 days. Two batches that were run in duplicate confirmed our initial results. A third enteral batch was run because of slight deviation in results for our second batch.

A concentration at time zero for injectable solution 1 was not obtained because of coordination difficulties between the laboratory and the pharmacy. No sample of enteral solution 1 was sent on day 90, and no samples for enteral solutions 2 and 3 were obtained on day 120 because of the small demand for the solution beyond the three-month period.

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Presented at the 18th Annual ASHP Midyear Clinical Meeting, Atlanta, Georgia, December 6, 1983.

Table 1.
Caffeine Concentrations[a] (mg/ml) in Injectable and Enteral Solutions

Sampling Day	Solution 1	Solution 2	Solution 3
Injectable			
0	. . .	9.9	. . .
30	10.2	9.7	. . .
60	9.9	11.0	. . .
90	10.2	9.1	. . .
120	9.2	9.6	. . .
Enteral			
0	9.5	8.6	10.8
14	10.1	9.0	10.0
30	10.4	10.0	10.0
60	9.7	9.6	11.2
90	. . .	8.7	11.4
120	10.0	. . .	. . .

[a] Concentrations reflect average value of each sample run; initial concentration was 10 mg/ml.

Tests for microbial growth were negative. Sterility testing is performed for each new lot of injectable caffeine that is compounded by the pharmacy; the product is quarantined for 14 days before use, to await final cultures.

Conclusion. Extemporaneously prepared solutions of citrated caffeine in sterile water and in syrup are stable for at least three months.

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Presented at the 18th Annual ASHP Midyear Clinical Meeting, Atlanta, Georgia, December 6, 1983.

Table 1.
Caffeine Concentrations[a] (mg/ml) in Injectable and Enteral Solutions

Sampling Day	Solution 1	Solution 2	Solution 3
Injectable			
0	...	9.9	...
30	10.2	9.7	...
60	9.9	11.0	...
90	10.2	9.1	...
120	9.2	9.6	...
Enteral			
0	9.5	8.6	10.8
14	10.1	9.0	10.0
30	10.4	10.0	10.0
60	9.7	9.6	11.2
90	...	8.7	11.4
120	10.0	...	...

[a] Concentrations reflect average value of each sample run; initial concentration was 10 mg/ml.

Tests for microbial growth were negative. Sterility testing is performed for each new lot of injectable caffeine that is compounded by the pharmacy; the product is quarantined for 14 days before use, to await final cultures.

Conclusion. Extemporaneously prepared solutions of citrated caffeine in sterile water and in syrup are stable for at least three months.

References

1. Aranda JV, Turman T. Methylxanthines in apnea of prematurity. *Clin Perinatol.* 1979; 6:87–108.
2. Anon. Benzyl alcohol toxicity: 16 deaths of neonates reported. *ASHP Signal.* 1982; 6:25, 31.
3. Ou CN, Frawley VL. Theophylline, dyphylline, caffeine, acetaminophen, salicylate, acetylsalicylate, procainamide, and *N*-acetyl procainamide determined in serum with a single liquid-chromatographic assay. *Clin Chem.* 1982; 28:2157–60.

REFLECTIONS

Pharmacist in paradise

GORDON G. MCGUIRE

Am J Hosp Pharm. 1984, 41 2406–9

One of the numerous inducements for entering the health profession is the idea that the universal need for health care allows an almost unlimited choice of places in which to practice. Unfortunately, opportunities to work in exotic settings are extremely rare and finding a position is more frequently a product of chance than of design.

This was true in my case. Practicing pharmacy on a tropical island in the Pacific was mere fantasy. The reality crept up on me. In the winter of 1979–80 while I was employed as a staff pharmacist at University of California–San Diego Medical Center, I heard about a pharmacy teaching position in Micronesia.

A Federal Health Manpower Development Grant had been funded that called for a multidisciplinary training program to be centered on Ponape in the Eastern Caroline Islands. It included a special provision from the National Health Service Corps (NHSC) to have a group of health-care professionals who could serve as on-site faculty. In all, the NHSC agreed to provide six practitioners—an internist, a pediatrician, an obstetrician-gynecologist, a surgeon, a dentist, and a pharmacist. Ultimately, all positions except the surgeon's were filled.

The program's funding allowed the practitioners to bring their families, some household goods, and a motor vehicle. My wife and 8-year-old son accepted this exotic adventure enthusiastically. My decision was finalized when the Medical Center agreed to grant me a two-year leave of absence, thus alleviating my concern about finding work when the adventure was over.

Island Living

The most dramatic realization my family and I made living in Micronesia was how many modern conveniences we took for granted living in California. Now, every time I turn on a light switch or a faucet, I marvel at how dependable these things are in the United States. During one three-month period in Ponape, we had electricity only from midnight until 7 a.m. because of a series of breakdowns among the island's electrical generators. Our telephone number had only three digits, never worked when it rained hard, and really was not very dependable in good weather either. Water, although a bit more reliable than electricity, was turned off every evening, making showering, dishwashing, and toilet flushing impossible after 8 p.m. Like the electricity, the water service also had shutdowns; however, they frequently lasted only several days.

GORDON G. MCGUIRE, PHARM. D., is a staff pharmacist, University of California-San Diego Medical Center, San Diego, CA 92103.

A. INGREDIENT NAME:

CANTHARIDIN

B. Chemical Name:

2,3 Dimethyl-7-Oxabicyclo [2.2.1.1 Heptane-2,3 Dicarboxylic Anhydride

C. Common Name:

Canthacur, Cantharone, Verr-Canth. Canthacur-PS; Cantharone Plus, Verrusol

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Result: The IR Spectrum exhibits the at WN>1800, which is typical of Anhydrides and it conforms with the data reported in literature [Stork, G:van Tamelen, E. et. al, J Am Chem Soc. 75, 388 (1953)]

E. Information about how the ingredient is supplied:

Colorless glistening or orthorhomibic plates, scales

F. Information about recognition of the substance in foreign pharmacopeias:

Span.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Rosenberg, E. W., Amonette, R. A., and Gardner, J. H. Cantharidin treatment of warts at home (letter). *Arch Dermatol,* 1977; 113(8):1134.

Harwell, W. B., Buchanan, Jr., R. N., and Hamilton, J. R. Foot Care. *J. Tennessee Med. Assoc.*, 1978;71:830.

Rosenberg, E. W., Amonette, R. A., and Gardner, J. H. Foot Care. *Arch. Dematol.*, 1977;113:1134.

H. Information about dosage forms used:

Liquid
Apply directly to the lesion and cover the growth completely.

I. Information about strength:

0.7%

J. Information about route of administration:

Topically

K. Stability data:

Melts at about 216-218°. Sublimes at about 110°with some fumes.
Stable

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

50-2635
#55160

CANTHARIDIN

2,3 DIMETHYL-7-OXABICYCLO [2.2.1.1 HEPTANE-2,3 DICARBOXYLIC ANHYDRIDE B

BATCH No. :2C/97

Appearance : Colorless glistening orthorhombic plates - E

Identification
Thin-Layer Chromatography

Silica Gel Plate Merck 6OF254
Eluent: CHI2Cl2MeOH: H2O=86.5:10:0.75
Detection: Iodine-saturated chamber: the spots are fixed with starch solution
Result: 1 single spot with Rf Ca. 0.76. The product is chromatographically pure.

Infrared spectrum:

Medium:KBr Tablet
Concentration: 1/300
Apparatus:Perkin-Elmer
D **Result:** The IR Spectrum exhibits the at WN>1800, which is typical of Anhydrides and it conforms with the data reported in literature [Stork. G:van Tamelen, E. et al, J Am Chem Soc. 75,388 (1953)]

GLC

Solution 0.1% in Ethyl Acetate, 4 microlitre are injected.
column: Chromosorb WMP 100/120 mesh,OV
17 3% (Methyl-Phenyl Silicone 50:50), length 2m.
Injector: 250C
Detector: 250C
Temperature: 120OC-1800C, 10OC/minute
Result: 1 single peak, no side peaks. The product is GLC-pure.

V

Melting point:	found 216°C, (sealed tube.	required uncorrected)	by BPC: 216-218°C
Residue on ignition negligible		required by BPC less than 0.1	per cent.

12/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: CANTHARIDIN _____

MANUFACTURE LOT NO.: 2C/97

PHYSICAL TEST

SPECIFICATION TEST STANDARD.:USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
COLORLESS GLISTENING OR ORTHORHOMBIC PLATES,SCALES.

2) SOLUBILITY.:
INSOLUBLE IN COLD WATER,SOMEWHAT SOLUBLE IN HOT WATER.ONE GRAM DISSOLVES IN 40ml ACETONE,65ml CHLOROFORM,560ml ETHER,150ml ETHYL ACETATE.SOLUBLE IN OILS.

3) MELTING POINT.:
MELTS AT ABOUT 216-218 degree.SUBLIMES AT ABOUT 110 degree WITH SOME FUMES.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES AS PER IR SPECTRUM CO.SPECS.

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

---------- IDENTIFICATION ----------

PRODUCT #: C7632 NAME: CANTHARIDIN

CAS #: 56-25-7

MF: C10H12O4

SYNONYMS

CAN * CANTHARIDES CAMPHOR * CANTHARIDIN * CANTHARIDINE * CANTHARONE *

EXO-1,2-CIS-DIMETHYL-3,6-EPOXYHEXAHYDROPHTHALIC ANHYDRIDE * 2,3-

DIMETHYL-7-OXABICYCLO(2.2.1)HEPTANE-2,3-DICARBOXYLIC ANHYDRIDE * 4,7-

EPOXYISOBENZOFURAN-1,3-DIONE, HEXAHYDRO-3A,7A-DIMETHYL-, (3A-ALPHA,4-

BETA,7-BETA,7A-ALPHA) * HEXAHYDRO-3A,7A-DIMETHYL-4,7-

EPOXYISOBENZOFURAN-1,3-DIONE * KANTHARIDIN (GERMAN) *

---------- TOXICITY HAZARDS ----------

RTECS NO: RN8575000

7-OXABICYCLO(2.2.1)HEPTANE-2,3-DICARBOXYLIC ANHYDRIDE, 2,3-DIMETHYL-

TOXICITY DATA

ORL-HMN LDLO:428 UG/KG 34ZIAG -,646,69

IPR-MUS LD50:1 MG/KG JAFCAU 35,823,87

REVIEWS, STANDARDS, AND REGULATIONS

IARC CANCER REVIEW:ANIMAL LIMITED EVIDENCE IMEMDT 10,79,76

IARC CANCER REVIEW:HUMAN NO ADEQUATE DATA IMEMDT 10,79,76

IARC CANCER REVIEW:GROUP 3 IMSUDL 7,56,87

EPA TSCA CHEMICAL INVENTORY, JUNE 1990

TARGET ORGAN DATA

CARDIAC (ARRYTHMIAS)

SKIN AND APPENDAGES (TUMORS)

TUMORIGENIC (NEOPLASTIC BY RTECS CRITERIA)

TUMORIGENIC (EQUIVOCAL TUMORIGENIC AGENT BY RTECS CRITERIA)

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

MAY BE FATAL IF INHALED, SWALLOWED, OR ABSORBED THROUGH SKIN.

VESICANT.

CAUSES BURNS.

MATERIAL IS EXTREMELY DESTRUCTIVE TO TISSUE OF THE MUCOUS MEMBRANES

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.
UNUSUAL FIRE AND EXPLOSIONS HAZARDS
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.
---------- REACTIVITY DATA ----------
STABILITY
STABLE.
CONDITIONS TO AVOID
LIGHT SENSITIVE
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
TOXIC FUMES OF:
CARBON MONOXIDE, CARBON DIOXIDE
HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.
---------- SPILL OR LEAK PROCEDURES ----------
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
EVACUATE AREA.
WEAR PROTECTIVE EQUIPMENT.
CAREFULLY SWEEP UP AND REMOVE.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.
WASTE DISPOSAL METHOD
INCINERATE IN A FURNACE PROVIDING ENVIRONMENTAL REGULATIONS PERMIT.
OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.
--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---
NIOSH/MSHA-APPROVED RESPIRATOR.
USE ONLY IN A CHEMICAL FUME HOOD.
COMPATIBLE CHEMICAL-RESISTANT GLOVES.
CHEMICAL SAFETY GOGGLES.
FACESHIELD (8-INCH MINIMUM).
VERY TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

CAUSES BURNS.
POSSIBLE RISK OF IRREVERSIBLE EFFECTS.
IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE

POSSIBLE).
WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.
DO NOT BREATHE DUST.
POSSIBLE CARCINOGEN.
VESICANT.

AND UPPER RESPIRATORY TRACT, EYES AND SKIN.
INHALATION MAY BE FATAL AS A RESULT OF SPASM, INFLAMMATION AND EDEMA
OF THE LARYNX AND BRONCHI, CHEMICAL PNEUMONITIS AND PULMONARY EDEMA.
SYMPTOMS OF EXPOSURE MAY INCLUDE BURNING SENSATION, COUGHING,

WHEEZING, LARYNGITIS, SHORTNESS OF BREATH, HEADACHE, NAUSEA AND

VOMITING.

CHRONIC EFFECTS

PROLONGED CONTACT CAN CAUSE:
CHEMICAL PNEUMONITIS.
PULMONARY EDEMA. EFFECTS MAY BE DELAYED.
SEVERE GASTROENTERITIS, NEPHRITIS, COLLAPSE, DEATH MAY OCCUR.*

POSSIBLE CARCINOGEN.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,
CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

ADDITIONAL INFORMATION

*MERCK INDEX, ELEVENTH EDITION (SIGMA PRODUCT M2404).

---------- PHYSICAL DATA ----------

MELTING PT: 216 TO 218'C
SOLUBILITY: ACETONE-SOLUBLE CHLOROFORM-SOLUBLE
WATER-INSOLUBLE

APPEARANCE AND ODOR

SOLID.

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.
WATER SPRAY.

Seatrace—Cont.

decongestant effect of pseudoephedrine on the swollen mucosa of the respiratory tract. Guaifenesin, an ether, is capable of being partially eliminated by way of the expired air, and is therefore able to exert a local expectorant action in the respiratory passages. Guaifenesin makes expectoration freer and easier, because the respiratory tract secretions are made more fluid and thereby more easily expelled.

Indications: Versacaps are indicated for the symptomatic relief of cough in conditions such as: the common cold, acute bronchitis, allergic asthma, broncholitis, emphysema, and tracheobrochitis. Versacaps are also indicated for relief of nasal congestion, chronic rhinitis, allergic rhinitis, and post nasal drip of chronic sinusitis.

Contraindications: Severe hypertension or severe cardiac disease, sensitivity to antihistamines or sympathomimetic agents.

Warnings: Use with caution in patients suffering from hypertension, cardiac disease or hyperthyroidism.

Precautions: Although pseudoephedrine hydrochloride causes virtually no pressor effect in normotensive patients, it should be used with caution in patients with hypertension.

Adverse Reactions: The great majority of patients will have no side effects. Only certain patients, sensitive to one or another of the ingredients, may note mild stimulation or mild sedation. As with other preparations containing antihistamines, drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Other side effects produced by antihistamine drugs include dizziness and dryness of the mouth. Gastrointestinal irritation has been reported.

Usual Adult Dosage: Two capsules every 12 hours; one capsule in mild cases.

Children 6–12: 1 capsule every 12 hours.

How Supplied: In bottles of 100 and 1000. Dispense in a tight, light resistant container as defined in the National Formulary.

Caution: Federal law prohibits dispensing without a prescription.

CONTAINS NO FD&C YELLOW DYE No. 5 (DYE FREE)

SERES Laboratories, Inc.

3331 INDUSTRIAL DRIVE
BOX 470
SANTA ROSA, CA 95402

CANTHARONE®

(cantharidin collodion)
For External Use Only

Description: CANTHARONE®, cantharidin collodion, is a topical liquid containing 0.7% cantharidin in a film-forming vehicle containing acetone, ethocel and flexible collodion. Ether 35%, alcohol 11%. The active ingredient, cantharidin, is a vesicant. The chemical name is Hexahydro-3aα, 7aα-dimethyl-4β, 7β-epoxyisobenzofuran-1, 3-dione. $C_{10}H_{12}O_4$

Clinical Pharmacology: The vesicant action of cantharidin is the result of its primary acantholytic action. Its effectiveness against warts is presumed to result from the "exfoliation" of the tumor as a consequence of its acantholytic action. The lytic action of cantharidin does not go beyond the epidermal cells, the basal layer remains intact and there is minimal effect on the corium; as a result there is no scarring from topical application.

Indications and Usage: Cantharone® is indicated for removal of warts and molluscum contagiosum. It is designed for topical application by a physician. Painless application and the absence of instruments makes it especially useful for treating children. See Dosage and Administration section for specific directions for use.

Contraindications: Cantharone® is not recommended for treatment of mosaic warts.

Warnings: Cantharidin is a strong vesicant and Cantharone® may product blisters if it comes in contact with normal skin or mucous membrane. If spilled on skin, wipe off at once, using acetone, alcohol or tape remover. Then wash vigorously with warm soapy water and rinse well. If spilled on mucous membrane or in eyes, flush with water, remove precipitated collodion, and flush with water for an additional 15 minutes. Residual pigment changes may occur. Patients vary in their sensitivity to cantharidin and in rare cases tingling, burning or extreme tenderness may develop. In these cases the patient should remove tape and soak the area in cool water for 10 to 15 minutes, repeating as required for relief. If soreness persists, puncture blister using sterile technique, apply antiseptic and cover with a Band-Aid. It is advisable to treat only one or two lesions on the first visit, until the sensitivity of the patient is known. For external use only.

Precautions: There have been no adequate and well-controlled studies on the use of cantharidin in pregnant women or nursing mothers, therefore the use of Cantharone® during pregnancy or in nursing mothers is not recommended.

Cantharone® is flammable; keep away from heat, sparks and flame.

Adverse Reactions: The development of annular warts following Cantharone® therapy has been reported in a small percentage of patients. These lesions are superficial and, although they may alarm some patients, present little problem. Treatment consists of patient reassurance and re-treatment using either Cantharone® or other procedures. There has been one report of chemical lymphangitis following use of Cantharone® in combination with salicylic acid plaster.

Dosage and Administration: *Ordinary and periungual warts*—No cutting or prior treatment is required. (Occasionally nails must be trimmed to expose subungual warts to medication.) Apply Cantharone® directly to the lesion; cover the growth completely using an applicator stick. Allow a few seconds for a thin membrane to form and cover with a piece of non-porous plastic adhesive tape e.g. Blenderm. Instruct patient to remove tape in 24 hours and replace with a loose Band-Aid. On next visit remove necrotic tissue and re-apply Cantharone® to any growth remaining. Defer second treatment if inflammation is intense. A single application may suffice for normally keratinized skin.

Plantar warts—Pare away keratin covering the wart: avoid cutting viable tissue. Using a Q-tip or applicator stick, apply Cantharone® to both the wart and a 1-3mm margin around the wart. Allow a few minutes to dry. Secure with non-porous plastic adhesive tape. Leave in place for a week, then debride. If any viable wart tissue remains after debridement, re-apply a small amount of Cantharone® and bandage as above. Three or more such treatments may be required for large lesions. When destruction of wart is complete, the healed site will appear smooth, with normal skin lines.

Palpebral warts—Using a toothpick or fine probe, apply a small amount of Cantharone® to the surface of the wart. Avoid touching surrounding normal skin or applying inside the eye lashes. Leave lesion uncovered. Repeat in a week or ten days if any growth remains.

Molluscum contagiosum—Coat each lesion with a thin film of Cantharone®. In one week, treat any new lesions the same way and retreat any resistant lesions with Cantharone®, this time covering with a small piece of occlusive tape. The tape should be removed in 6 to 8 hours.

How Supplied: 7.5 mL bottle (096-01). Close tightly immediately. Keep away from heat.
Revised Sept. 1982
Direct inquiries to Kathryn

CANTHARONE PLUS™

For External Use Only

Description: CANTHARONE topical liquid containing 30% 5% podophyllin, 1% cantharidin forming vehicle containing 0.5% polyethylene glycol, cellosolve dion, castor oil and acetone. Salicylic acid is a deratolytic name is 2-Hydroxybenzoic acid a caustic. It is an extract of the roots of Podophyllum peltatum a vesicant, the chemical name 3aα, 7aα-dimethyl-4β, 7β-epoxy 1, 3-dione.

How Supplied: 7.5 mL bottle (097-01). Close tightly immediately. Keep away from heat. Do not
Revised Sept. 1982
Direct inquiries to Kathryn

Serono Laboratories

280 POND STREET
RANDOLPH, MA 02368

Serono Laboratories, Inc. will answer inquiries about the following

ASELLACRIN®

(somatropin)

FOR INTRAMUSCULAR INJECTION

Description: Asellacrin (somatropin) sterile, lyophilized, purified somatropin extracted from the human gland.

The potency of Asellacrin (somatropin) is determined by bioassay in hypophysectomized rats and is designated in International Units (IU). Each 10 ml vial contains 10 IU somatropin and 40 mg of mannitol. After reconstitution, each milliliter of Asellacrin contains 2 IU of somatropin and 4 mg mannitol as well as other pituitary hormones as shown below:

Follitropin (FSH)	less than 0.0
Lutropin (LH)	less than 17.85 IU
Corticotropin (ACTH)	less than .014 IU
Thyrotropin (TSH)	less than 0.0
Prolactin (PRL)	less than 2.86 IU

The pH is adjusted between 6 and 8 with hydrochloric acid and/or sodium hydroxide.

Clinical Pharmacology:

A. Skeletal Growth

Asellacrin (somatropin) stimulates linear growth in patients with pituitary growth hormone deficiency. The measurable increase in growth (body length) after somatropin administration results from its effect on cartilaginous growth areas of the long bones. It is believed that somatropin's effect is mediated by a growth factor, or somatomedin which permits the incorporation of sulfate into cartilage. Somatomedin is low in serum of the growth hormone deficient patients whose growth hormone deficiency is the result of hypopituitarism or hypophysectomy, whereas its presence can be demonstrated after somatropin therapy.

B. Cellular Growth

In addition to its effect on the skeleton, somatropin brings about an increase in the muscle and visceral mass. In muscle tissue the increase in mass is observed by a corresponding increase in number and dimension of muscle fiber cells.

(842-w)

...iano; Cannab.; Cannabis Indica; Chanvre; ...dian Hemp.

...3-14-7.

...bis has also been known as: *Ait makhlif, Aliam-*, Anhascna, Assyuni, Bambalacha, Bambia, Ban-, Bangue, Bhang, Bhangaku, Canapa, Canhama, Cannacoro, Can-Yac, Caroçuda, Chur, Chutsao, Da-boa, Dacha, Dagga, Darakte-, Dirijo, Djamba, Djoma, Dokka, Donajuanita, Durijo, Elva, Erva maligna, Erva do norte, Esrar, Finote, Fokkra, Fumo brabo, Fumo de cabo-, Ganga, Ganja, Ganjila, Gnaoui, Gongo, Gozah, ...dool, Greefe, Grifa, Guabza, Guaza, Gunjah, Haouzi, Hen-Nab, Hursini, Hashish, Igbo, In-, ...ptruid, Indisk hampa, Intianhamppu, Intsangu, Jatiphaladya churna, Jea, Juana, Kanab, Kar-, Kanh-Chha, Khanje, Kif, Kif Ktami, Kinnab, Li-, Maconha, Maconia, Madi, Magiyam, Makhlif, ...angango, Marajuana, Marigongo, Marihuana, Mariquita, Maruamba, Matekwane, Mbanje, Misari, Mnoana, Momea, Mota, Mulatinha, Mun-, Namba, Ntsangu, Nwonkaka, Peinka, Penek, Pot, Pretinha, Rafe, Rafi, Rafo, Riamba, Rongo-, Rosa Maria, Sabsi, Sadda, Siddhi, Soñadora, Sous-, Suruma, Tahgalim, Takrouri, Teriaki, Tronadora, Umya, Urumogi, Wee, ...ba, Yoruba, Zacate chino, Zerouali, and Ziele ...jskich.

...and approximate synonyms for cannabis resin in-, Charas, Charris, Chira, Churrus, Chus, Ga-, ...wiche, Garoarsch, Gauja, *Hachiche*, Hascisc, ...isis, Hasji's, Hasjisj, Haszysz, Haxixe, Heloua, Malak, Manzul, Momeka, *N'rama*, and *Sighirma*.

...ics. In *Chin.*

...flowering or fruiting tops of the pistillate plant of ...tiva (Cannabinaceae). In the UK cannabis is de-...as any part of any plant of the genus *Cannabis*. ...sually refers to a mixture of the leaves and flow-, *Bhang, dagga, ganja, kif,* and *maconha* are com-...ed in various countries to describe similar ... *Hashish* and *charas* are names often applied to ...although in some countries *hashish* is applied to any ...preparation.

...cannabinoids has been extracted from the drug, the ...rtant being Δ^9-tetrahydrocannabinol (dronabinol), ...drocannabinol, Δ^9-tetrahydrocannabinolic acid, ..., and cannabidiol. Cannabinol and cannabidiol ...present in large amounts but have little activity. The ...of Δ^9-tetrahydrocannabinol may average 1, 3, and 5% ..., ganja, and hashish respectively.

...dence

...reported that the prolonged heavy use of cannabis ...to tolerance and psychic dependence but that phys-...dence had not been demonstrated. There have been ...reports of non-specific symptoms such as anorex-, insomnia, irritability, restlessness, sweating, head-... mild gastro-intestinal upsets occurring when ...is withdrawn.

...se Effects

...and vomiting may be the first effects of cannabis tak-...oth. The most frequent physical effects of cannabis ...on are an increase in heart rate with alterations in ...ssure, injected conjunctival vessels, and deteriora-...motor coordination. The psychological effects include ...distortion of time and space, irritability, and distur-...of memory and judgement. Anxiety or panic reactions ..., particularly in inexperienced users. Psychotic ep-...of a paranoid or schizophrenic nature, and usually ...have occurred in subjects taking cannabis, especially in ...ses or after the use of varieties bred for a high yield of ...noids (so-called skunk).

...reviews of the adverse effects of cannabis.

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... S. Cannabis and cocaine. *Pharm J* 1993; **251**: 483–5.

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...ancy and the neonate. Cannabis has effects on ... and can alter reproductive hormonal systems. Infants ... mothers exposed to cannabis during pregnancy tend ... a lower birth-weight[1,2] and may suffer from increased ... in the postnatal period.[3]

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Psychosis. References to psychosis associated with cannabis.

1. Rottanburg D, *et al.* Cannabis-associated psychoses with hypomanic features. *Lancet* 1982; **ii**: 1364–6.
2. Andréasson S, *et al.* Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *Lancet* 1987; **ii**: 1483–6.
3. Wylie AS, *et al.* Psychosis due to "skunk". *Br Med J* 1995; **311**: 125.

Treatment of Adverse Effects

Mild panic reactions do not usually require specific therapy; reassurance is generally sufficient. Diazepam may be necessary for severe reactions.

Flumazenil was effective in reversing coma in 2 children who had ingested cannabis.[1]

1. Rubio F, *et al.* Flumazenil for coma reversal in children after cannabis. *Lancet* 1993; **341**: 1028–9.

Precautions

Cannabis has been reported to affect driving. Cannabis and alcohol have additive effects; interactions might be expected between cannabis and a wide range of drugs.

Interactions. Antimuscarinic agents, including tricyclic antidepressants, may produce additive increases in heart rate[1] whereas conversely propranolol tends to attenuate cannabis-induced tachycardia. Limited evidence indicates that a combination of disulfiram and cannabis may produce a hypomanic state.[2] For a suggestion that cannabis smoking can increase the clearance of theophylline, see p.1661.

1. Hillard JR, Vieweg WVR. Marked sinus tachycardia resulting from the synergistic effects of marijuana and nortriptyline. *Am J Psychiatry* 1983; **140**: 626–7.
2. Lacoursiere RB, Swatek R. Adverse interaction between disulfiram and marijuana: a case report. *Am J Psychiatry* 1983; **140**: 243–4.

Pharmacokinetics

The active principles of cannabis are absorbed from the gastro-intestinal tract and the lungs.

About 50% of the Δ^9-tetrahydrocannabinol available in cannabis is present in the smoke inhaled from a whole cannabis cigarette. This produces an effect almost immediately, reaches a peak in 20 to 30 minutes, and is dissipated in about 3 to 4 hours. When cannabis is taken by mouth absorption may be slow and irregular. Effects are not seen for 30 minutes to 1 hour and persist for about 8 hours.

Tetrahydrocannabinol is lipophilic and becomes widely distributed in the body. It is extensively metabolised, primarily in the liver, to the active 11-hydroxy derivative; both are extensively bound to plasma proteins. It is excreted in the urine and faeces, sometimes over prolonged periods. Excretion may be more rapid in chronic users.

Pregnancy and the neonate. Cannabinoids cross the placenta[1] and are excreted in breast milk.[2] For the effects of cannabis on the neonate, see above.

1. Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. *Clin Pharmacokinet* 1995; **28**: 235–69.
2. American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics* 1994; **93**: 137–50.

Uses and Administration

Cannabis was formerly employed as a sedative or narcotic. Its main active constituent Δ^9-tetrahydrocannabinol (dronabinol, see p.1218) and a synthetic cannabinol (nabilone, see p.1230) are used as antiemetics in patients receiving cancer chemotherapy; they are also being investigated for a number of other potential therapeutic uses. Anecdotal reports exist of benefit from cannabis in a variety of disorders including glaucoma, malignant neoplasms, multiple sclerosis, and AIDS.

References to the potential medical uses of cannabis.

1. Doyle E, Spence AA. Cannabis as a medicine? *Br J Anaesth* 1995; **74**: 359–61.
2. Gray C. Cannabis—the therapeutic potential. *Pharm J* 1995; **254**: 771–3.
3. Grinspoon L, Bakalar JB. Marihuana as a medicine: a plea for reconsideration. *JAMA* 1995; **273**: 1875–6.
4. Wills S. The use of cannabis in multiple sclerosis. *Pharm J* 1995; **225**: 237–8.

Canola Oil (17665-l)

Canola oil is a form of rape oil (see p.1748) from strains selected for low erucic acid content. It is used as an edible oil and in pharmaceutical manufacturing and cosmetics.

Cantharides (12517-g)

Blistering Beetle; Cantharis; Insectes Coléoptères Hétéromères; Lytta; Méloides; Russian Flies; Spanish Fly.

The dried beetle *Cantharis vesicatoria* (=*Lytta vesicatoria*) (Meloidae) or other spp., containing not less than 0.6% of cantharidin.

Adverse Effects

Following ingestion of cantharides there is burning pain in the throat and stomach, with difficulty in swallowing; nausea, vomiting, haematemesis, abdominal pain, bloody diarrhoea, and tenesmus; renal pain, frequent micturition, haematuria, uraemia; severe hypotension and circulatory failure. Oral doses of cantharidin (the active ingredient of cantharides) of less than 65 mg have been lethal. A dose of 1 mg or contact with one insect can produce distressing symptoms. Skin contact results in blisters.

References.

1. Hundt HKL, *et al.* Post-mortem serum concentration of cantharidin in a fatal case of cantharides poisoning. *Hum Exp Toxicol* 1990; **9**: 35–40.

Uses and Administration

Preparations of cantharides have been employed externally as rubefacients, counter-irritants, and vesicants. They should not be taken internally or applied over large surfaces owing to the risk of absorption. The use of cantharides in cosmetic products is prohibited in the UK by law.

Cantharides is used in homoeopathic medicine.

Mylabris (Chinese blistering beetle; Chinese cantharides; Indian blistering beetle), the dried beetles of the species *Mylabrus sidae* (= *M. phalerata*), *M. cichorii*, and *M. pustulator*, has been used as a substitute for cantharides and as a source of cantharidin (see below) in the East.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Multi-ingredient preparations. *Spain:* Frikton.

Cantharidin (12518-q)

Hexahydro-3a,7a-dimethyl-4H,7H-epoxyisobenzofuran-1,3-dione.

$C_{10}H_{12}O_4$ = 196.2.

CAS — 56-25-7.

Cantharidin is obtained from cantharides or mylabris (see above under Cantharides).

Cantharidin in flexible collodion has been applied for the removal of warts. It has also been used in veterinary medicine. Owing to the high toxicity of cantharidin it is recommended that preparations containing it should not be used medicinally. Adverse effects are those described for Cantharides (see above).

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Canad.: Canthacur; Cantharone; *USA:* Cantharone†; Verr-Canth.

Multi-ingredient preparations. *Canad.*: Canthacur-PS; Cantharone Plus; *USA:* Cantharone Plus†; Verrusol.

Capsicum (4617-w)

Capsic.; Capsici Fructus; Chillies; Piment Rouge; Pimentão; Spanischer Pfeffer.

CAS — 404-86-4 (capsaicin).

NOTE. Ground cayenne pepper of commerce is normally a blend of varieties. Paprika is from *Capsicum annuum* var. *longum*; it is milder than capsicum.

Pharmacopoeias. In *Aust., Ger., Hung., It., Jpn,* and *Swiss.*

US includes capsicum oleoresin.

The dried ripe fruits of *Capsicum annuum* var. *minimum* and small-fruited varieties of *C. frutescens* (Solanaceae). Some pharmacopoeias allow different varieties. It contains not less than 0.5% of the pungent principle capsaicin. **Store** in a cool dry place. Protect from light.

Capsicum Oleoresin (USP 23) is an alcoholic extract of capsicum. It is a dark red oily liquid. **Soluble** in alcohol, in acetone, in ether, in chloroform, and in volatile oils; soluble with opalescence in fixed soils. **Store** in airtight containers.

Capsicum has a carminative action but it is mainly used externally, often in the form of capsicum oleoresin, as a counter-irritant. However, preparations of capsicum and capsicum oleoresin can be very irritant. Capsaicin (p.28), the active ingredient of capsicum, is also used in topical preparations in the treatment of painful skin conditions.

Capsicum is also used in homoeopathic medicine and in cookery.

No acceptable daily intake was established for paprika oleoresin as the daily intake of this spice extract was considered to be self-limiting.[1]

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 789* 1990.

1-d

cium Pidolate. The calcium salt of 5-yrrolidine-2-carboxylic acid.
$(C_5H_6NO_3)_2$=296.3.
cium pidolate is used as a source of calcium.
rietary Names
(Millot-Solac, Fr.).

2-n

cium Sucrose Phosphate. A mixture g the approximate empirical formula of the m salt of a monophosphate ester of sucrose.
$H_{21}CaO_{14}P,2H_2O$=496.4.
S — *12676-30-1; 25584-76-3 (both anhyd-*

cium sucrose phosphate has been used in the ention of dental caries.
eviews of its use in preventing dental caries, see *Br. J.*, 1968, *1*, 267; *Lancet*, 1968, *1*, 1187; G. G. *Br. dent. J.*, 1975, *138*, 25.

3-h

cium Sulfexanoate. The calcium salt of -dithiodi(hexanoic acid).
$H_{20}CaO_4S_2$=332.5.
S — *22414-93-3.*
cium sulfexanoate has been used in the treat- of hepatic disorders.
rietary Names
(Berna, Ital.); Lipexal *(Berna, Spain).*

4-m

mphoscapine. Noscapine Camsylate.
capine camphor-10-sulphonate.
$H_{23}NO_7,C_{10}H_{16}O_4S$=645.7.
S — *25333-79-3.*
mphoscapine is used for the relief of cough.
rietary Names
an *(Logeais, Fr.).*
The name Tulisan has also been used for thiram..

5-b

mptothecin.
$H_{16}N_2O_4$=348.4.
S — *7689-03-4.*
alkaloid from *Camptotheca acuminata* (Nys- ae). Pale yellow crystals. M.p. 264° to 267° decomposition.
mptothecin has antineoplastic activity.
eview of the biogenesis, synthesis, and pharmacology camptothecin.— M. Shamma and V. St. Georgiev, *J. m. Sci.*, 1974, *63*, 163.
rief review of the antileukaemic properties of camp- ecin.— M. E. Wall and M. C. Wani, *A. Rev. Phar- & Toxic.*, 1977, *17*, 117.

6-v

nella *(B.P.C. 1934).* White Cinnamon; Wild namon Bark.
S — *8022-43-3 (canella oil).*
bark of *Canella alba* (= *C. winterana*) nellaceae), containing a bitter principle and ut 1% of a volatile oil.
nella is a mild aromatic bitter. A mixture of powdered bark with aloes is known as Hiera ra and has been used as an emmenagogue.

7-g

ntharides *(B.P.C. 1949).* Cantharis; Blister- Beetle; Lytta; Russian Flies; Spanish Fly; ectes Coléoptères Hétéromères; Méloides.
rmacopoeias. In *Aust.*, *Hung.*, *Nord.*, *Port.*, and *Swiss.*

The dried beetle *Cantharis vesicatoria* (= *Lytta vesicatoria*) (Meloidae) or other spp., containing not less than 0.6% of cantharidin. **Store** in airtight containers. Protect from light. Cantharides having an ammoniacal odour should not be used.

Adverse Effects. Following ingestion of cantharides there is burning pain in the throat and stomach, with difficulty in swallowing; nausea, vomiting, colic, bloody diarrhoea, and tenesmus; renal pain, frequent micturition, haematuria; chill, syncope, and circulatory failure. Toxic effects have been produced by 600 mg, and death by 1.5 to 3 g, though recovery has occurred from much larger doses.

Acute cantharides intoxication in a 20-year-old man.— A. J. Presto and E. C. Muecke, *J. Am. med. Ass.*, 1970, *214*, 591.

Treatment of Adverse Effects. Empty the stomach by inducing emesis or by aspiration and lavage; activated charcoal and sodium sulphate have been recommended; give demulcent drinks freely (but *not* oils or fats) and morphine for pain; hot applications to the abdomen may relieve the pain. The circulation should be maintained by the intravenous infusion of plasma or of suitable electrolyte solutions.

Uses. Preparations of cantharides have been employed externally as rubefacients, counter-irritants, and vesicants. They should not be taken internally or applied over large surfaces owing to the risk of absorption.
Cantharides is used in homoeopathic medicine.

12518-q

Cantharidin *(B.P.C. 1949, B. Vet. C. 1965).* Hexahydro-3aα,7aα-dimethyl-4β,7β-epoxyisobenzofuran-1,3-dione.
$C_{10}H_{12}O_4$=196.2.
CAS — 56-25-7.
Pharmacopoeias. In *Span.*

Cantharidin is obtained from cantharides (see above) or mylabris (see p.1730). It occurs as colourless, odourless, glistening crystals which sublime at about 120°. M.p. 216° to 218°.
Very slightly **soluble** in water; soluble 1 in about 1100 of alcohol, 1 in 40 of acetone, 1 in 55 of chloroform, 1 in 700 of ether, and 1 in 150 of ethyl acetate; soluble in fixed oils.

Cantharidin was formerly used as a counter-irritant and vesicant and was usually preferred to cantharides since the strength of preparations could be more readily controlled. Preparations of cantharidin were used in hair lotions for their rubefacient action. Cantharidin in flexible collodion has been applied for the removal of warts. It has also been used in veterinary medicine. Owing to the high toxicity of cantharidin it is recommended that preparations containing it should not be used medicinally. Adverse effects and treatment are those described for Cantharides (see above). The fatal dose is less than 60 mg.

For reports of fatalities after accidental poisoning with cantharidin, see *Pharm. J.*, 1953, *2*, 467; L. C. Nickolls and D. Teare, *Br. med. J.*, 1954, *2*, 1384; J. D. Craven and A. Polak, *ibid.*, 1386; M. A. Lécutier, *ibid.*, 1399.

A 42-year-old man took a teaspoonful of a preparation containing approximately 20 mg of cantharidin. He developed symptoms of renal damage which responded to treatment including a magnesium sulphate enema and high fluid intake of milk. Hydrocortisone pellets were effective against mouth ulcers.— R. D. Rosin, *Br. med. J.*, 1967, *4*, 33.

An 18-year-old woman who swallowed about 2 ml of a preparation containing cantharidin (Cantharone) developed electrocardiographic changes indicative of myocardial damage, in addition to local effects in the mouth, throat, and pharynx, which responded to treatment with hydrocortisone sodium succinate and with ampicillin, given parenterally.— W. B. Ewart *et al.* (letter), *Can. med. Ass. J.*, 1978, *118*, 1199.

Proprietary Names
Cantharone *(Seres, USA).*

12519-p

Caoutchouc. Cautchuc; Elastica; Kautschak; Gummi Elasticum; Resina Elastica; Rubber *(B.P.C. 1934)*; India-Rubber.
CAS — 9006-04-6.

The principal constituent of the coagulated latex obtained chiefly from the trunks of *Hevea brasiliensis* (Euphorbiaceae).
A yellowish-white to brown elastic material with a characteristic odour. Almost completely **soluble** in chloroform; partially soluble in petroleum ether.

Caoutchouc is used pharmaceutically in the manufacture of adhesive plasters.

Allergic contact sensitivity to thiuram compounds (present in rubber) in patients in a haemodialysis unit.— N. S. Penneys *et al.*, *Archs Derm.*, 1976, *112*, 811.

Contact urticaria to rubber.— A. F. Nutter, *Br. J. Derm.*, 1979, *101*, 597.

12520-n

Capobenic Acid. C-3. 6-(3,4,5-Trimethoxybenzamido)hexanoic acid.
$C_{16}H_{23}NO_6$=325.4.
CAS — 21434-91-3.

Capobenic acid is a vasodilator which has been used in the prevention and treatment of myocardial infarction and other cardiac disorders.

Proprietary Names
Cardiobiol *(Lifepharma, Spain)*; Cardiobiomar *(Bio-Mar, Spain)*; C-Tre (sodium salt) *(Ist. Chem. Ital., Ital.)*; Kelevitol *(Migra, Arg.)*; Pectoris *(Llorens, Spain)*; Trifartine *(Phoenix, Arg.).*

12521-h

Carazolol. BM-51052. 1-(Carbazol-4-yloxy)-3-isopropylaminopropan-2-ol.
$C_{18}H_{22}N_2O_2$=298.4.
CAS — 57775-29-8.

Carazolol is a beta-adrenoceptor blocking agent.

Pharmacology of carazolol in *animals.*— W. Bartsch *et al.*, *Arzneimittel-Forsch.*, 1977, *27*, 1022.

Proprietary Names
Conducton *(Klinge, Ger.).*

12522-m

Carbadox. GS-6244. Methyl 3-(quinoxalin-2-ylmethylene)carbazate N^1N^4-dioxide.
$C_{11}H_{10}N_4O_4$=262.2.
CAS — 6804-07-5.

A yellow crystalline powder. M.p. about 245°. Practically **insoluble** in water.

Carbadox is an antibacterial agent used in veterinary practice for treating swine dysentery and enteritis and for promoting growth.

Manufacturers
Pfizer, UK.

12523-b

Carbamylglutamic Acid. *N*-Carbamoyl-L-glutamic acid.
$C_6H_{10}N_2O_5$=190.2.
CAS — 1188-38-1.

Carbamylglutamate has been used in the treatment of hyperammonaemia.

References to the use of carbamylglutamate with arginine in the treatment of hyperammonaemia.— C. Bachmann *et al.* (letter), *New Engl. J. Med.*, 1981, *304*, 543.

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*6

TITLE:	**Cantharidin treatment of warts at home [letter]**
AUTHOR:	**Rosenberg EW; Amonette RA; Gardner JH**
SOURCE:	**Arch Dermatol 1977 Aug;113(8):1134**
NLM CIT. ID:	**77240911**
MAIN MESH SUBJECTS:	**Cantharidin/*ADMINISTRATION & DOSAGE/THERAPEUTIC USE Warts/*DRUG THERAPY**
ADDITIONAL MESH SUBJECTS:	**Human Self Administration**
PUBLICATION TYPES:	**LETTER**
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CANTHARIDIN

Actions:

Pharmacology: Effectiveness against warts is presumed to result from the "exfoliation" of the tumor as a consequence of its acantholytic action. The lytic action of cantharidin does not go beyond the epidermal cells, the basal layer remains intact, and there is minimal effect on the corium; as a result, there is no scarring from topical application.

Indications:

A vesicant for removal of benign epithelial growths: Warts (including ordinary, periungual, subungual and plantar) and molluscum contagiosum.

Contraindications:

Diabetics or persons with impaired peripheral circulation; use on eyes, mucous membranes, ano-genital or intertriginous areas, moles, birthmarks or unusual warts, hair growing from them, or if lesion is being treated with other agents; if growth or surrounding tissue is inflamed or irritated.

Warnings:

Vesicant properties: Cantharidin is a strong vesicant. Use sparingly. Do not use in ano-genital area. Keep away from eyes and mucosal tissue. Avoid use in intertriginous sites due to problems with spreading and body occlusion which often lead to more intense, painful reactions.

Cantharidin may produce blisters on normal skin or mucous membranes. If spilled on skin, wipe off at once, using acetone, alcohol or tape remover; wash with warm soapy water and rinse well. If spilled on mucous membranes or in eyes, flush with water, remove precipitated collodion; flush with water for an additional 15 minutes.

Physician use (application) only: Cantharidin is a potent vesicant and should be applied only by a physician. It is not to be dispensed to the patient.

Sensitivity: Patients vary in sensitivity to cantharidin; tingling, burning or extreme tenderness may develop rarely. In these cases, remove tape and soak the area in warm water for 10 to 15 minutes; repeat as required for relief. If soreness persists, puncture blister aseptically, apply antiseptic and cover with bandage. Treat only one or two lesions on the first visit, until the sensitivity of the patient is known. Expect more intense reaction in patients with fair skin and blue eyes. Do not reapply to same lesion more than once per week. Defer second treatment if inflammation is intense.

Palpebral warts: Use great care if treating palpebral warts. Make certain film is thoroughly dry; warn patient not to touch the eyelid.

Pigmentation: Although rare, use care in the selection of site application since pigmentation changes may occur.

Pregnancy: There have been no adequate and well controlled studies in pregnant women; therefore, the use of cantharidin during pregnancy is not recommended.

Lactation: Use in nursing mothers is not recommended.

Adverse Reactions:

Annular warts have occurred in some patients. These are superficial and present no problem, although they may alarm patients. Reassure patient and treat again.

There have been several reports of chemical lymphangitis following use of cantharidin, one in combination with salicylic acid plaster. A case of extreme, painful blistering occurred after treatment of multiple axillary lesions.

Patient Information:

May cause tingling, itching or burning within a few hours after application; site may be extremely tender for 2 to 6 days.

If spilled on skin, wipe off at once with acetone, alcohol or tape remover and wash with soap and water.

For external use only. If spilled in the eyes, flush with water and contact physician.

Administration and Dosage:

Ordinary and periungual warts: No cutting or prior treatment is required. Apply directly to the lesion and cover the growth completely, extending beyond by about 1 mm. Allow a few minutes for a thin membrane to form. Cover completely with nonporous tape. Remove tape in 24 hours and replace with a loose bandage. On next visit (1 to 2 weeks), remove necrotic tissue and reapply to any remaining growth. Defer second treatment if inflammation is intense. A single treatment frequently suffices.

CANTHARIDIN

Plantar warts: Pare away keratin covering the wart; avoid cutting viable tissue. Apply to wart and 1 to 3 mm around the wart. Allow to dry, secure with nonporous tape; application of a protective cut-out cushion over the tape may be helpful. After 24 hours, the patient may bathe and replace dressing. Debride 1 to 2 weeks after treatment. If any viable wart tissue remains, reapply as above; ≥ 3 treatments may be required for large lesions. For large mosaic warts, treat a portion of the wart at a time. Applying cantharidin to open tissue will result in stinging from the solvent. Avoid by paring carefully and scheduling treatments 2 weeks apart.

Molluscum contagiosum: Apply a very small amount of solution to only the top of each lesion. Let dry completely. No occlusive tape or dressing is needed. Alert patient that blistering is the desired result and that temporary hypopigmentation may occur. The patient may bathe after 4 to 6 hours; sooner if discomfort occurs. Blisters are usually formed by about 24 hours and crust up in about 4 days. Mild discomfort or itching can usually be controlled with bathing and night sedation. In 1 week, treat new or remaining lesions the same way and re-treat any resistant lesions. This time, cover with a small piece of occlusive tape. Remove tape in 4 to 6 hours, sooner if discomfort occurs.

Note: Use of a mild antibacterial is recommended until the tissue re-epithelializes.

Rx	**Verr-Canth** (Palisades)	**Liquid:** 0.7% cantharidin in an adherent film-forming base of ethylcellulose, cellosolve, castor oil, penederm (octylphenylpolyethylene glycol), acetone	In 7.5 ml.	2952

KERATOLYTIC COMBINATIONS

Rx	**Verrex** (Palisades)	**Liquid:** 30% salicylic acid and 10% podophyllum in an adherent film-forming vehicle of penederm (octylphenylpo-lyethylene glycol), ethylcellulose, cello-solve, collodion, castor oil, acetone	In 7.5 ml with applicator.	1086
otc	**Gets-It** (Oakhurst)	**Liquid:** Salicylic acid, zinc chloride and collodion in ~35% ether and ~28% alcohol	In 12 ml.	150

and should not be used for long periods of time (57). The FDA advisory panel concluded, however, that there was no evidence to establish that zinc chloride contributes significantly to corn-callus removal when combined with salicylic acid compared to a single-entity salicylic acid product. Thus, the zinc chloride-salicylic acid combination was classified as a Category III combination. Further, the panel was concerned about the possible formation of zinc salicylate (pharmacologically inactive) when these two drugs are contained in a product and established that stability testing be undertaken as part of the Category III testing (44).

Agents Used to Treat Warts

Ascorbic Acid Although ascorbic acid is essential to the development of supporting tissue (collagen and intracellular ground substance) and healing, there are insufficient data available to establish its efficacy in topical wart therapy (38). The panel has recommended further study of ascorbic acid before it can be considered effective for nonprescription use (38).

Calcium Pantothenate Application of the alcohol derivative pantothenol in various ulcerative and pyogenic dermatoses stimulates epithelialization and allays itching. There have been no reports of sensitization or allergic reaction to topical therapy with pantothenic acid or its derivatives (58). The use of these drugs in adults and children seems safe. Topical formulations contain 2–5% of the active pantothenic acid derivative. However, there are insufficient data available on the effectiveness of this agent. Thus, the panel classified calcium pantothenate as Category III (38).

Cantharidin Cantharidin is a potent vesicant available by prescription only as an ingredient of Cantharone. For wart therapy, this liquid is applied lightly with a stick or swab, allowed to dry, and then covered by a piece of waterproof adhesive tape slightly larger than the wart (41). Depending on the physician's directions, the bandage is left in place between 24 hours and 1 week and then removed. The drug effects a separation at the dermal-epidermal junction and therefore the removal of the epidermal-residing wart (35). Following the blister formation, minor inflammation can be resolved with tap water soaks (35).

In approximately 7–14 days, a blister, often hemorrhagic, which has formed will break, crust, and fall off. At this time, the physician debrides the dead material with fine-curved iris scissors (50). Since the effect of cantharidin is entirely intraepidermal, no scarring ensues.

A disadvantage of cantharidin is that, on occasion, annular warts may develop at the blister periphery (24). In addition, since this method is considered dangerous, it should be performed only by a physician or podiatrist and never by the patient at home (50). However, a successful trial of cantharidin treatment of warts at home has been reported (59). Application of the occlusive tape was omitted from the instruction to simplify the process and produce fewer reactions. This mode demonstrated an easy, safe, and reasonably effective means of treating warts. To help facilitate correct application of this product, some investigators advocate that the product be colored by the addition of some green food coloring dye (35).

Podophyllum Podophyllum resin (in concentrations of up to 25%) dispensed in compound benzoin tincture or as a solution in alcohol is effective in the treatment of condyloma acuminatum (genital warts). Podophyllum should not be prescribed for inclusion into a flexible collodion vehicle because of the collodion's occlusive nature and the possibility of enhancement of the drug's percutaneous absorption. It is a cytotoxic agent that arrests mitosis in metaphase. This caustic and powerful skin irritant is available by prescription only for short-term use. It may be reapplied every 4–7 days, generally for 2–4 weeks, depending on individual response and any residual chemical irritation (22). In 24–48 hours after application, lesions become necrotic, and in the following days, begin to slough off and gradually disappear.

The primary toxicologic problem associated with the use of podophyllum resin, aside from its topical irritant qualities, is peripheral neuropathy when it is absorbed percutaneously into the systemic circulation (60). Podophyllum should be applied only in small amounts by the physician. The patient should be instructed to wash off the podophyllum preparation with soap and water within 8–12 hours of its application. Because the usual delivery system is a low-viscosity suspension (compound tincture of benzoin) or tincture (alcohol), the solution tends to run onto adjacent tissue, causing damage. This risk may be minimized if white petrolatum or talc is applied to the healthy surrounding skin before the podophyllum preparation is applied to the wart (22, 35).

Podophyllum resin for vulvar warts in pregnant women should be used cautiously, if at all. The topical application of podophyllum applied five times for 4 hours each from the 23rd to the 29th week of pregnancy was suspected of causing teratogenic effects (61). Because of this encountered difficulty with podophyllum, and to prevent the possible development of laryngeal papillomatosis in the neonate after delivery, the physician should consider using cryosurgery to remove the venereal wart or deliver the neonate by caesarean section (18). Podophyllum should not be used on hemorrhaging skin or where an extensive skin surface area is involved. These conditions increase the possibility of percutaneous absorption. Because podophyllum is a potent corrosive, it should not be used with other keratolytic agents, such as salicylic acid.

Miscellaneous Prescription Drugs Used to Treat Warts Other prescription drugs used fairly successfully in treating warts are the antibiotic bleomycin sulfate (Blenoxane) for recurrent or recalcitrant plantar warts, tretinoin (retinoic acid) for flat warts and plantar warts (62-64), and fluorouracil (65). Although bleomycin has not been approved by the FDA for wart treatment, evidence indicates that bleomycin's effectiveness

is due to the drug's selective inhibition of DNA synthesis. In addition, local injection into the wart results in hemorrhagic necrosis secondary to microthrombosis, which is followed by a gradual reduction and detachment of the wart (66). Theoretical objection to the use of bleomycin for warts stems from its ability to interfere with DNA metabolism and induce skin cancer (67). One report indicated the appearance of nail dystrophy following the injection of bleomycin into a periungual wart (66). Results with tretinoin and fluorouracil therapy are variable and, in those cases that do respond, it has not been determined whether the disease is simply taking its natural course (41). Idoxuridine 0.25% ointment demonstrated efficacy in the treatment of six women suffering from condyloma acuminatum (68). The drug was applied twice daily for one week. No side effects were observed and there were no recurrences in these women three months after followup. One precaution however, with idoxuridine is that it has induced congenital anomalies in animals and thus its safety for use to treat genital warts during pregnancy remains in doubt.

Adjunctive Therapy

In addition to nonprescription products, self-therapy measures include daily soaking of the affected area throughout treatment for at least 5 minutes in very warm (not hot) water to remove dead tissue (24). Dead tissue should be removed gently after normal washing. Skin should not be removed forcibly because further damage could result. Sharp knives or razor blades that have not been properly sterilized should not be used to cut dead tissue because they may cause bacterial infection. A rough towel, callus file, or pumice stone effectively removes dead tissue of corns and calluses. Petroleum jelly should be applied to the healthy skin surrounding the affected area to avoid accidental application of corrosive products. This precaution is especially important in cases where poor eyesight increases the chances of misapplication.

To relieve painful pressure emanating from inflamed underlying tissue and irritated or hypertrophied bones directly underneath a corn or callus, patients may use a pad such as Dr. Scholl's with an aperture for the corn or callus. If the skin can tolerate the pads, they may be used up to 1 week or longer (69). To prevent the pads from adhering to hosiery, patients may wax the pads with paraffin or a candle and powder them daily with a hygienic foot powder. If, despite these measures, friction causes the pads to peel up at the edge and stick to hosiery, the pharmacist may recommend that patients cover their toes with the forefoot of an old stocking or pantyhose before putting on hosiery (69).

Patients should be advised that if at any time the pad begins to cause itching, burning, or pain, it should be removed and a podiatrist should be consulted. The pharmacist also should advise the patient that these pads will provide only temporary relief and rarely cure a corn or a callus.

To avoid the spread of warts, which are contagious, patients should wash their hands before and after treating or touching wart tissue, and a specific towel should be used only for drying the affected area after cleaning. Patients should not probe or poke the wart tissue. Footwear should be worn in the case of plantar warts. If warts are present on the sole of the foot, patients should not walk in bare feet unless the wart is securely covered.

Product Selection Guidelines

Corns and Calluses

There are no clinical studies to indicate whether prescription-only products are superior to nonprescription products. Conclusions are based only on subjective physician evaluation reports (2, 9). Salicylic acid in a plaster or collodion dosage form appears to be the most effective treatment for corns and calluses. Some studies advocate the use of a 50% silver nitrate solution, applied by the physician, followed by weekly applications of 40% salicylic acid plasters for corns (7, 9).

Bunions

If the pharmacist recommends the use of topical adhesive cushioning to alleviate the pressure on a bunion, instructions should be given on proper use. Before the protective pad is applied, the foot should be bathed and dried thoroughly. The pad then is cut into a shape that conforms to the bunion. If the intent is to relieve the pressure from the center of the bunion area, the pad can be cut to surround the bunion. Precut pads are available for immediate patient use. Constant skin contact with adhesive-backed pads should be avoided, unless under a podiatrist, or other physician's recommendation.

Warts

Opinions about the best wart treatment vary from nitric acid for plantar warts to cantharidin preparations for common warts (41, 70). The findings of the FDA advisory review panel on nonprescription miscellaneous external drug products clarified the effectiveness and safety of nonprescription drugs (38, 53).

In an evaluation of four plantar wart products, a dimethylbenzylammonium dibromide solution (Callusolve paint) was less effective than either a 50% podophyllum resin-liquid paraffin preparation or an established salicylic paint [salicylic acid-lactic acid-collodion preparation (1:1:4)] (34). A flexible collodion was used as the control preparation. The study also showed that the basic treatment for simple plantar warts takes about 6 weeks, and the cure rate was fastest with the salicylic paint. It was concluded that the treatment of plantar warts with a salicylic acid-lactic acid-flexible collodion mixture was enhanced when the application method was understood and was carried out under a physician's supervision.

The salicylic acid-lactic acid-flexible collodion preparation used in this study was safe and effective in children and adults; no incidences of hypersensitivity or systemic involvement were reported. Podophyllum also was used with no acute reactions, but it was under the direct supervision of a physician, and the therapy was

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National Library of Medicine: IGM Full Record Screen

TITLE: Efficacy of intra-arterial norcantharidin in suppressing tumour 14C-labelled glucose oxidative metabolism in rat Morris hepatoma.

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SOURCE: HPB Surg 1996;10(2):65-72

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ABSTRACT: Norcantharidin is the demethylated form of Cantharidin, which is the active ingredient of the blister beetle, Mylabris, a long used Chinese traditional medicine. Though not well publicized outside China, Norcantharidin is known to possess significant anti-hepatoma activity, and is relatively free from side effects. In the present study, glucose oxidation in tumour and liver tissue slices harvested from hepatoma-bearing animals was quantified by measuring the radioactivity of 14C-labelled CO2 released from 14C-glucose in oxygen-enriched incubation medium. Results were expressed as a tumour/liver ratio. For comparison, treatments with Norcantharidin, Adriamycin and with hepatic artery ligation were studied. The mean tumour/liver ratio was 4.2 +/- 2.2 in untreated controls, but dropped significantly to 2.3 +/- 0.5 ($p < 0.05$) with intra-arterial Norcantharidin (0.5 mg/kg) and to 2.3 +/- 0.7 ($p < 0.05$) with intra-arterial Adriamycin (2.4 mg/kg), and to 2.2 +/- 0.7 ($p < 0.05$) with hepatic artery ligation. However, with intravenous Adriamycin at 2.4 mg/kg, the mean tumour/liver ratio was reduced to only 3.5 +/- 2.0 and was not significantly different from untreated controls. It is concluded that intra-arterial Norcantharidin is as effective as intraarterial Adriamycin and hepatic artery ligation in suppressing tumour glucose oxidative metabolism. These result simply that Norcantharidin may have a role to play in the chemotherapy of primary liver cancer.

MAIN MESH SUBJECTS:	**Antineoplastic Agents/*THERAPEUTIC USE** **Bicyclo Compounds, Heterocyclic/*THERAPEUTIC USE** **Carbon Radioisotopes/*METABOLISM** **Carcinoma, Hepatocellular/*DRUG THERAPY/METABOLISM** **Glucose/*METABOLISM** **Liver Neoplasms, Experimental/*DRUG THERAPY/METABOLISM**
ADDITIONAL MESH SUBJECTS:	**Animal** **Antibiotics, Anthracycline/THERAPEUTIC USE** **Comparative Study** **Doxorubicin/THERAPEUTIC USE** **Drug Screening** **Hepatic Artery/SURGERY** **Infusions, Intra-Arterial** **Ligation** **Male** **Oxidation-Reduction** **Rats** **Rats, Inbred BUF** **Support, Non-U.S. Gov't**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Antibiotics, Anthracycline)** **0 (Antineoplastic Agents)** **0 (Bicyclo Compounds, Heterocyclic)** **0 (Carbon Radioisotopes)** **23214-92-8 (Doxorubicin)** **50-99-7 (Glucose)** **5442-12-6 (norcantharidin)**

A. INGREDIENT NAME:

CYCLANDELATE

B. Chemical Name:

Alpha-Hydroxy-, 3,3,5-Trimethylcylclohexyl Ester (9CI), BS 572, Capilan, Ciclospasmol, Alpha-Hydroxybenzeneacetic Acid 3,3,5-Trimethylcyclohexyl Ester,, Sancyclan, Sepyron, 3, 3, 5-Trimethylcyclohexanol, Alpha-Phenyl-Alpha-Hydroxyaxetate, 3,5,5-Trimethylcyclohexyl Amygdalate, 3,3,5-Trimethylcyclohexyl Mandelate, Methylcyclohexyl Mandelate.

C. Common Name:

Arto-Espasmol, Perebral, Saiclate
Cyclobral, Spasmione, Spasmocyclon, Spasmocyclone
Cyclospansmol
Benzenenacetic Acid, Clandilon, Cyclandelate, Cyclolyt, Cyclomandol, Cyclospasmol,

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay 99.8%

E. Information about how the ingredient is supplied:

A white to off-white amorphous powder with a slight menthol-like odor and a bitter taste.

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

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Capote, B. and Parikh. *J. Am. Geriat. Soc.*, 1978; 26:360.

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Cunha-Vaz, J. G. Diabetic Retinopathy. *Br. J. Ophthal.* 1977; 61:399.

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Hester, T. O., Theilman, G., and Green, W. Cyclandelate in the management of tinnitus: a randomized, placebo-controlled study. *Otolaryngol Head Neck Surg,* 1998; 118(3Pt1): 329-332.

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Gerber, W. D., Schellenberg, R., and Thom, M. Cyclandelate versus popranolol in the prophylaxis of migraine–a double-blind placebo-controlled study. *Funct Neurol*, 1995; 10(1):27-35.

Mota, M. C., Leite, E., and Ruan, M.A. Effect of cyclospasmol on early diabetic retinopathy. *Int Opthalmol*, 1987; 10(1):3-9.

H. Information about dosage forms used:

Capsules
Tablets
Suspension

I. Information about strength:

1.6g daily
400 mg Tablets and Capsules
400 mg/5ml Suspension

J. Information about route of administration:

Oral or Intravenous

K. Stability data:

Melts at about 50-53°
Cyclandelate can decompose by hydrolysis to mandelic acid.
Cyclandelate capsules concluded that less that 5% of the cyclandelate degraded in 66 months at ambient temperatures.

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-7981
#50838
#51878

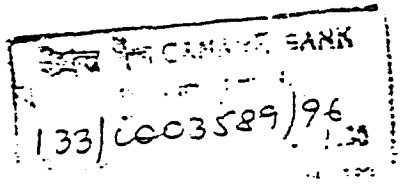
1.	PRODUCT	CYCLANDELATE
2.	BATCH NO.	279076
3.	DATE OF MANUFACTURING	JULY 15, 1996
4.	QUANTITY	150 KGS
5.	PACKING	HDPE DRUMS
6.	DESCRIPTION	WHITE AMORPHOUS POWDER HAVING FAINT CAMPHOR LIKE ODOUR & BITTER TASTE. FREELY SOLUBLE IN METHANOL.
7.	MELTING POINT	56°C
8.	IDENTIFICATION	POSITIVE
9.	LOSS ON DRYING	0.27% (limit 0.5%)
10.	RESIDUE ON IGNITION	0.058% (limit 0.1%)
11.	ASSAY	99.8%
12.	RESULT	THE SAMPLE PASSES IN ALL TESTS.

6/97

FOR R.L CHEMICAL INDUSTRIES PVT. LTD.

SATYAPAL GUPTA
TECHNICAL DIRECTOR

DATE: JULY 18, 1996



QUALITY CONTROL REPORT

CHEMICAL NAME.: CYCLANDELATE _____

MANUFACTURE LOT NO.: 279076

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.: WHITE POWDER.

2) SOLUBILITY.:
PRACTICALLY INSOLUBLE IN WATER; SOLUBLE IN LIPOIDS AND THEIR SOLVENTS; SOLUBILITY IN MEOH 1/20 IS CLEAR.

3) MELTING POINT.:
MELTS AT ABOUT 50-53 DEGREES.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES WITH IR AS PER COMPANY SPECIFICATIONS.

PASSES.: _____ **FAILS.:** _____

COMMENTS.: CYCLANDELATE IS ALSO KNOWN AS MANDELIC ACID 3,3,5 TRIMETHYLCYCLO-HEXYLESTER.

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

---------- IDENTIFICATION ----------

PRODUCT #: C9260 NAME: CYCLANDELATE CRYSTALLINE

CAS #: 456-59-7

MF: C17H24O3

SYNONYMS

ARTO-ESPASMOL * BENZENEACETIC ACID, ALPHA-HYDROXY-, 3,3,5-TRIMETHYLCYCLOHEXYL ESTER (9CI) * BS 572 * CAPILAN * CICLOSPASMOL *

CLANDILON * CYCLANDELATE * CYCLOLYT * CYCLOMANDOL * CYCLOSPASMOL *

DILATAN * ALPHA-HYDROXYBENZENEACETIC ACID 3,3,5-TRIMETHYLCYCLOHEXYL ESTER * PEREBRAL * SAICLATE * SANCYCLAN * SEPYRON * SPASMIONE * SPASMOCYCLON * SPASMOCYCLONE * 3,3,5-TRIMETHYLCYCLOHEXANOL ALPHA-PHENYL-ALPHA-HYDROXYACETATE * 3,5,5-TRIMETHYLCYCLOHEXYL AMYGDALATE *

3,3,5-TRIMETHYLCYCLOHEXYL MANDELATE *

---------- TOXICITY HAZARDS ----------

RTECS NO: OO8200000

MANDELIC ACID, 3,3,5-TRIMETHYLCYCLOHEXYL ESTER

TOXICITY DATA

ORL-RAT LD50:5 GM/KG	NIIRDN 6,310,82
IPR-RAT LD50:2570 MG/KG	AIPTAK 105,145,56
ORL-MUS LD50:>10 GM/KG	NIIRDN 6,310,82
IPR-MUS LD50:3780 MG/KG	AIPTAK 105,145,56
IPR-DOG LD50:2000 MG/KG	AIPTAK 105,145,56
ORL-GPG LD50:3950 MG/KG	AIPTAK 105,145,56
IPR-GPG LD50:2480 MG/KG	AIPTAK 105,145,56

REVIEWS, STANDARDS, AND REGULATIONS

NOES 1983: HZD X4828; NIS 1; TNF 42; NOS 2; TNE 457; TFE 234

EPA TSCA CHEMICAL INVENTORY, JUNE 1990

TARGET ORGAN DATA

BEHAVIORAL (ALTERED SLEEP TIME)

BEHAVIORAL (ATAXIA)

LUNGS, THORAX OR RESPIRATION (OTHER CHANGES)

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.

MAY CAUSE IRRITATION.

MAY CAUSE FLUSHING, TINGLING, SWEATING, NAUSEA, GASTRO-INTESTINAL

DISTRESS, HEADACHES, TACHYCARDIA, FEELING OF WEAKNESS
TARGET ORGAN(S):
SMOOTH MUSCLE
VASCULAR SYSTEM
THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR

SOLID.

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

STABILITY

STABLE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

CARBON MONOXIDE, CARBON DIOXIDE

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR PROTECTIVE EQUIPMENT.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.
WASTE DISPOSAL METHOD
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.
--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---
WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT
GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.
MECHANICAL EXHAUST REQUIRED.
CAUTION:
AVOID CONTACT AND INHALATION.
TARGET ORGAN(S):
SMOOTH MUSCLE
VASCULAR SYSTEM
THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

Nylidrin Hydrochloride Tablets *(U.S.P.)*. Tablets containing buphenine hydrochloride. Store in airtight containers.

Proprietary Names

Arlibide *(US Vitamin, Arg.)*; Arlidin *(USV, Canad.; USV Pharmaceutical Corp., USA)*; Bufedon *(Cedona, Neth.)*; Dilatol *(Tropon, Ger.)*; Dilydrin *(Medichemie, Switz.)*; Opino *(Bayropharm, Ital.)*; Penitardon *(Woelm, Ger.)*; Pervadil *(ICN, Canad.)*; Tocodrin *(Medichemie, Switz.)*.

Buphenine hydrochloride was formerly marketed in Great Britain under the proprietary name Perdilatal Forte *(Smith & Nephew Pharmaceuticals)*.

9215-s

Butalamine Hydrochloride. LA 1221. *NN*-Dibutyl-*N'*-(3-phenyl-1,2,4-oxadiazol-5-yl)ethylenediamine hydrochloride.

$C_{18}H_{28}N_4O.HCl = 352.9$.

CAS — 22131-35-7 (butalamine); 56974-46-0 (hydrochloride).

A white crystalline powder. M.p. 135° to 141°. **Soluble** 1 in 7 of water, 1 in 10 of alcohol, and 1 in 2.5 of chloroform.

Butalamine hydrochloride is a vasodilator which has been given in the treatment of peripheral vascular disorders.

Proprietary Names

Adrevil *(Zyma, Ger.)*; Hemotrope *(Andromaco, Arg.)*; Surem *(CEPA, Spain)*; Surheme *(Aron, Fr.; Spemsa, Ital.)*.

9216-w

Butoxyethyl Nicotinate. 2-Butoxyethyl nicotinate.

$C_{12}H_{17}NO_3 = 223.3$.

CAS — 13912-80-6.

Butoxyethyl nicotinate is a topical vasodilator used, in a concentration of 2.5%, in rubefacient ointments.

Proprietary Preparations

See under Methyl Nicotinate, p.1626..

9217-e

Cetiedil Citrate. 2-(Perhydroazepin-1-yl)ethyl α-cyclohexyl-α-(3-thienyl)acetate dihydrogen citrate monohydrate.

$C_{20}H_{31}NO_2S.C_6H_8O_7.H_2O = 559.7$.

CAS — 14176-10-4 (cetiedil); 16286-69-4 (citrate, anhydrous).

Cetiedil citrate is a vasodilator which has been given in the treatment of peripheral vascular disorders.

After intravenous injection of radioactively labelled cetiedil, 50% of the dose was metabolised within 5 minutes, and after 1 hour only labelled metabolites were recovered from the urine. Cetiedil was also shown to be rapidly metabolised after administration by mouth, and after first pass through the liver only metabolites would enter the general circulation. It was concluded that the metabolites of cetiedil were active as inhibition of saliva secretion persisted when cetiedil could no longer be detected in plasma.— A. M. Soeterboek *et al., Eur. J. clin. Pharmac.*, 1977, *12*, 205.

Asthma. References to bronchodilator activity of cetiedil citrate: J. Orehek *et al., Nouv. Presse méd.*, 1976, *5*, 1577; Y. W. Cho *et al., Int. J. clin. Pharmac. Biopharm.*, 1978, *16*, 402.

Peripheral vascular disorders. An evaluation of cetiedil, administered intravenously, intramuscularly, or by mouth, in the treatment of peripheral vascular disorders.— R. Barbe *et al., Clin. Trials J.*, 1980, *17*, 20.

Proprietary Names

Stratene *(Innothéra, Fr.; Sigmatau, Ital.)*.

9218-l

Chromonar Hydrochloride. Carbocromen Hydrochloride; A27053; AG 3; Cassella 4489. Ethyl 3-(2-diethylaminoethyl)-4-methylcoumarin-7-yloxyacetate hydrochloride.

$C_{20}H_{27}NO_5.HCl = 397.9$.

CAS — 804-10-4 (chromonar); 655-35-6 (hydrochloride).

A white crystalline powder with a bitter taste. M.p. about 159°. **Soluble** in water, alcohol, and chloroform.

Chromonar hydrochloride is a vasodilator which has been used in the prophylaxis of angina pectoris.

For reports of pharmacological studies, see R. E. Nitz and E. Potzsch, *Arzneimittel-Forsch.*, 1963, *13*, 243; W. Lochner and H. Hirche, *ibid.*, 251; H. J. Bretschneider *et al., ibid.*, 255.

Absorption, blood concentrations, and excretion of chromonar.— Y. C. Martin and R. -G. Wiegand, *J. pharm. Sci.*, 1970, *59*, 1313.

Cardiac disorders. A multicentre double-blind crossover study of 187 patients with angina pectoris who received chromonar for 8 weeks (79 patients) or 12 weeks (108 patients) at a dosage of 150 mg thrice daily (73 patients) or 225 mg thrice daily (114 patients) demonstrated significant prevention of anginal attacks by the lower dose, and improvement in attack-rate and glyceryl trinitrate requirement by the higher dose although the higher dose failed to show any advantage over placebo when the glyceryl trinitrate requirement was considered alone.— R. J. Bing *et al., Clin. Pharmac. Ther.*, 1974, *16*, 4. See also H. Bell *et al., ibid.*, 1968, *9*, 40.

Further references: G. Faucon *et al., Thérapie*, 1975, *30*, 185; E. Schraven, *Arzneimittel-Forsch.*, 1976, *26*, 197; E. Schraven *et al., ibid.*, 200; R. Sirbulescu *et al., ibid.*, 204; N. N. Kipsidze and G. M. Kikava, *ibid.*, 1976, *26*, 882.

Proprietary Names

Antiangor *(ISM, Ital.)*; Cardiocap *(Fidia, Ital.)*; Cromene *(Scharper, Ital.)*; Intensain *(Cassella-Riedel, Belg.; Diamant, Fr.; Cassella-Riedel, Ger.; Pierrel, Ital.; Jap.;Boehringer Mannheim, S.Afr.; Albert-Farma, Spain; Cassella-Riedel, Switz.)*; Intensacrom *(Albert-Farma, Spain)*.

9219-y

Cinepazet Maleate. Cinepazic Acid Ethyl Ester Maleate. Ethyl 4-(3,4,5-trimethoxycinnamoyl)piperazin-1-ylacetate hydrogen maleate.

$C_{20}H_{28}N_2O_6.C_4H_4O_4 = 508.5$.

CAS — 23887-41-4 (cinepazet); 50679-07-7 (maleate).

A white powder. M.p. 130°.

Cinepazet maleate is a vasodilator which has been used in the treatment of angina pectoris.

Absorption and fate of cinepazet in man. Most of a dose given by mouth was eliminated within 24 hours, 60% being excreted in the urine. The major metabolite was cinepazic acid.— L. F. Chasseaud *et al., Arzneimittel-Forsch.*, 1972, *22*, 2003.

Proprietary Names

Vascoril *(Delalande, Belg.; Delalande, Fr.; Delalande, Ital., Delalande, Switz.)*.

9220-g

Cinepazide Maleate. 1-(Pyrrolidin-1-ylcarbonylmethyl)-4-(3,4,5-trimethoxycinnamoyl)piperazine hydrogen maleate.

$C_{22}H_{31}N_3O_5.C_4H_4O_4 = 533.6$.

CAS — 23887-46-9 (cinepazide); 26328-04-1 (maleate).

Cinepazide maleate is a vasodilator which has been given in peripheral and cerebral vascular disorders and in coronary insufficiency.

Pharmacology in *animals*.— B. Pourrias *et al., Thérapie*, 1974, 29, 29 and 43.

Proprietary Names

Vasodistal *(Delalande, Fr.; Delalande, Ital.; Delalande, Switz.)*.

9221-q

Cloridarol. Clobenfurol. α-(Benzofuran-2-yl)-α-(4-chlorophenyl)methanol.

$C_{15}H_{11}ClO_2 = 258.7$.

CAS — 3611-72-1.

A white odourless crystalline powder. M.p. about 48°.

Cloridarol has been given in the prevention and treatment of coronary insufficiency.

Proprietary Names

Cordium *(Massone, Arg.)*; Menacor *(Menarini, Ital.)*; Menoxicor *(Menarini, Spain)*.

9222-p

Cyclandelate. BS 572. 3,3,5-Trimethylcyclohexyl mandelate.

$C_{17}H_{24}O_3 = 276.4$.

CAS — 456-59-7.

A white to off-white amorphous powder with a slight menthol-like odour and a bitter taste. M.p. below 60°. On storage it may sublime into a crystalline form resembling cotton wool.

Practically **insoluble** in water; soluble 1 in about 1 of alcohol and 1 in about 2 of light petroleum; very soluble in ether and other common organic solvents. **Store** in a cool place in airtight containers. Protect from light.

Adverse Effects. Nausea, gastro-intestinal distress, or flushing may follow high doses of cyclandelate.

Other adverse effects reported include tingling and headache.

Toxicity of cyclandelate was low, though with large doses there might be flushing, tingling, nausea, or headache.— T. Winsor and C. Hyman, *Clin. Pharmac. Ther.*, 1961, *2*, 652.

Treatment of Adverse Effects. In severe overdosage the stomach should be emptied by aspiration and lavage. If necessary the circulation should be maintained with infusions of suitable electrolytes, and if necessary by vasopressors.

Precautions. Cyclandelate is contra-indicated in the acute phase of a cerebrovascular accident.

Uses. Cyclandelate is a vasodilator used in the treatment of cerebrovascular and peripheral vascular disorders. It is given in a dosage of 1.6 g daily in divided doses.

Action. *Animal* studies into the mode of action of cyclandelate: A. B. H. Funcke *et al., Curr. med. Res. Opinion*, 1974, *2*, 37 (brain glucose uptake); G. van Hell, *Curr. med. Res. Opinion*, 1974, *2*, 211 (collateral vessel formation).

Cerebrovascular disease. Several double-blind studies of cyclandelate have shown improvement in orientation, disturbed behaviour, and vocabulary without improvement in self-care, recent memory, or mood. Nevertheless, the overall results are inconsistent, and improvements in clinical and psychological tests are not always matched by useful changes in the activities of daily living.— *Br. med. J.*, 1978, *2*, 348. See also *Drug & Ther. Bull.*, 1975, *13*, 85. Further reviews: *Med. Lett.*, 1976, *18*, 38; P. Cook and I. James, *New Engl. J. Med.*, 1981, *305*, 1508 and 1560.

Individual reports and studies on the role of cyclandelate in cerebrovascular disease: J. Young *et al., Br. J. Psychiat.*, 1974, *124*, 177; P. Hall, *J. Am. Geriat. Soc.*, 1976, *24*, 41; G. Davies *et al., Age and Ageing*, 1977, *6*, 156; D. B. Rao *et al., J. Am. Geriat. Soc.*, 1977, *25*, 548; R. Brasseur, *Angiology*, 1978, *29*, 121; B. Capote and N. Parikh, *J. Am. Geriat. Soc.*, 1978, *26*, 360; G. F. A. Harding *et al., Angiology*, 1978, *29*, 139; L. Sourander and C. B. Blakemore, *ibid.*, 133.

Diabetic retinopathy. In a double-blind randomised study deterioration of the blood-retinal barrier was assessed in 22 diabetic patients, without retinal involvement, by vitreous fluorophotometry after the injection of fluorescein. It was considered that deterioration of the blood-retinal barrier, an early sign of diabetic retinopathy, was delayed in the third month in those patients given cyclandelate 400 mg four times daily for 3 months. Long-term studies were considered to be indicated.— J. G. Cunha-Vaz *et al., Br. J. Ophthal.*, 1977,

61, 399.

Dysmenorrhoea. Over a period of 15 years, 60 women with spasmodic dysmenorrhoea had been treated with cyclandelate with consistently good results; 800 mg daily in divided doses was given for 3 days before the expected date of menstruation and for the first 2 days of menstruation.— D. Kerslake (letter), *Br. med. J.*, 1973, *2*, 614.

Peripheral vascular disease. A review of drugs used in the management of peripheral vascular disease, including cyclandelate. There is no substantial evidence to recommend the use of cyclandelate in peripheral vascular diseases.— J. D. Coffman, *New Engl. J. Med.*, 1979, *300*, 713. Further references: R. E. Fremont, *Am. J. med. Sci.*, 1964, *247*, 182; T. Reich, *J. Am. Geriat. Soc.*, 1977, *25*, 202.

Proprietary Preparations

Cyclobral *(Norgine, UK)*. Cyclandelate, available as capsules of 400 mg.

Cyclospasmol *(Brocades, UK)*. Cyclandelate, available as **Capsules** of 400 mg; as **Suspension** containing 400 mg in each 5 ml; and as **Tablets** of 400 mg. (Also available as Cyclospasmol in *Austral., Belg., Canad., Denm., Fr., Neth., Norw., S.Afr., Switz., USA*).

Other Proprietary Names

Arto-Espasmol *(Spain)*; Ciclospasmol *(Ital.)*; Cyclomandol *(Swed.)*; Spasmocyclon *(Ger.)*; Vasodyl *(Spain)*.

9223-s

Di-isopropylammonium Dichloroacetate. DIPA; Di-isopropylamine Dichloroethanoate; Di-isopropylamine Dichloroacetate.
$C_8H_{17}Cl_2NO_2 = 230.1$.

CAS — 660-27-5.

Crystals with an odour of chlorine and a slightly bitter taste. M.p. 119° to 121°. **Soluble** 1 in less than 2 of water; very soluble in alcohol and chloroform.

Di-isopropylammonium dichloroacetate is a vasodilator which has been given in the treatment of peripheral and cerebral vascular disorders.

A review of the pharmacology and therapeutic effects of di-isopropylammonium dichloroacetate.— P. W. Stacpoole, *J. clin. Pharmac.*, 1969, *9*, 282.

Proprietary Names
Cubisol *(Piam, Ital.)*; Dedyl *(Difrex, Austral.; Houdé-I.S.H., Fr.)*; Diedi *(Atem, Belg.; ISF, Ital.; Seber, Spain)*; Kalodil *(Fidia, Ital.)*; Neovascoril *(Saita, Ital.)*; Nutricor *(Llorens, Spain)*; Vasculene *(Von Boch, Ital.)*.

9224-w

Dilazep Hydrochloride. Asta C 4898. Perhydro-1,4-diazepin-1,4-diylbis(trimethylene 3,4,5-trimethoxybenzoate) dihydrochloride.
$C_{31}H_{44}N_2O_{10}.2HCl = 677.6$.

CAS — 35898-87-4 (dilazep); 20153-98-4 (hydrochloride).

Dilazep hydrochloride is a vasodilator which has been given in the treatment of coronary insufficiency and angina pectoris.

Pharmacology in *animals*.— D. Leuke *et al.*, *Arzneimittel-Forsch.*, 1972, *22*, 639. Toxicity studies in *animals*.— H. H. Able *et al.*, *ibid.*, 667; H. Schriewer and H. M. Rauen, *ibid.*, 1455.

The myocardial blood flow was measured in 5 patients with catheterised hearts given dilazep and found to be increased after doses of 160 to 310 µg per kg bodyweight.— I. Hensel *et al.*, *Arzneimittel-Forsch.*, 1972, *22*, 652. Evidence of coronary vascularisation induced by dilazep in *animals*.— G. Schmidt *et al.*, *ibid.*, 663.

Metabolism.— E. Schaumlöffel and R. Prignitz, *Arzneimittel-Forsch.*, 1972, *22*, 1651.

For a series of papers on the pharmacology and use of dilazep in ischaemic heart disease, see *Arzneimittel-Forsch.*, 1974, *24*, 1851 to 1926.

The effects of dilazep on blood platelet aggregation.— F. Kuzuya, *Arzneimittel-Forsch.*, 1979, *29*, 539.

Proprietary Names
Cormelian *(Asta, Ger.; Schering, Ital.)*; Komerian *(Jap.)*.

9225-e

Diltiazem Hydrochloride. Latiazem Hydrochloride; CRD-401. *cis*-(+)-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one hydrochloride.
$C_{22}H_{26}N_2O_4S.HCl = 451.0$.

CAS — 42399-41-7 (diltiazem); 33286-22-5 (hydrochloride).

A white odourless crystalline powder with a bitter taste. M.p. about 212° with decomposition. Freely **soluble** in water, chloroform, and methyl alcohol; slightly soluble in dehydrated alcohol. **Protect** from light.

Diltiazem hydrochloride exists in 2 crystalline forms: prisms and plates.— K. Kohno *et al.*, *Arzneimittel-Forsch.*, 1977, *27*, 1424.

Diltiazem hydrochloride is a vasodilator which has been used in the management of angina pectoris.

Animal pharmacology studies of diltiazem: D. Saito *et al.*, *Arzneimittel-Forsch.*, 1977, *27*, 1669; Y. Ito *et al.*, *Br. J. Pharmac.*, 1978, *64*, 503.

Cardiac disorders. *Angina pectoris.* References: R. Kusukawa *et al.*, *Arzneimittel-Forsch.*, 1977, *27*, 878; I. Nakayama, *Int. J. clin. Pharmac. Biopharm.*, 1979, *17*, 410.

Heart failure. The effect of diltiazem hydrochloride on sodium diuresis and renal function in chronic congestive heart failure.— M. Kinoshita *et al.*, *Arzneimittel-Forsch.*, 1979, *29*, 676.

Hypoglycaemia. Diltiazem hydrochloride 44 mg given intravenously over 2 hours to a woman with hypoglycaemic attacks due to an insulinoma reduced insulin secretion for the first 10 minutes but also reduced the blood-glucose concentration. A dose of 180 mg daily by mouth for 15 days reduced the frequency of attacks.— H. Taniguchi *et al.* (letter), *Lancet*, 1977, *2*, 501.

Proprietary Names
Herbesser *(Jap.)*; Masdil *(Esteve, Spain)*.

9226-l

Dipyridamole. RA 8. 2,2′,2″,2‴-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinittrilo]tetraethanol.
$C_{24}H_{40}N_8O_4 = 504.6$.

CAS — 58-32-2.

An odourless, intensely yellow, crystalline powder with a bitter taste. Solutions have a yellowish-blue fluorescence. M.p. about 163°.
Very slightly **soluble** in water; soluble in chloroform, methyl alcohol, and dilute acids; slightly soluble in acetone; practically insoluble in ether and light petroleum.

Adverse Effects. Gastric disturbances, diarrhoea, headache, dizziness, faintness, and skin rash may occur after administration of dipyridamole. Some patients experience facial flushing and a bitter taste after intravenous injection. Rapid intravenous injection of dipyridamole may cause a lowering of blood pressure, especially in patients with hypertension. Dipyridamole can also induce angina in some patients.

Alopecia. A 38-year-old woman with the haemolytic-uraemic syndrome initially treated with streptokinase and heparin, was subsequently treated with aspirin 3 g daily and dipyridamole 300 mg daily. Alopecia during treatment might have been due to dipyridamole.— J. A. Utting and D. R. Shreeve, *Br. med. J.*, 1973, *2*, 591.

Effects on the heart. Comment on the role of dipyridamole in myocardial scintigraphy, including mention that a rather unexpected effect of distal coronary vasodilators is angina, which may be reversed by glyceryl trinitrate or, in severe cases, aminophylline.— *Lancet*, 1980, *2*, 1346.

Precautions. Dipyridamole should be given only with care to patients with hypotension and should not be given to patients with hypotension following myocardial infarction.

Interactions. In 24 patients with glomerulonephritis who were stabilised on either warfarin or phenindione, dipyridamole in doses up to 400 mg daily did not affect prothrombin activity. It was recommended that when dipyridamole was used the prothrombin activity should be maintained at the upper end of the therapeutic range in order to avoid possible bleeding complications due to the slight anticoagulant activity of dipyridamole.— S. Kalowski and P. Kincaid-Smith, *Med. J. Aust.*, 1973, *2*, 164.

Interference with diagnostic tests. Serum from a patient taking dipyridamole gave very high readings when lipoproteins were being measured by nephelometry. Dipyridamole imparts a yellowish-blue fluorescence to solutions and could interfere in other laboratory tests involving fluorescence or nephelometry measurements.— K. Wiener (letter), *Lancet*, 1981, *2*, 634.

Pregnancy and the neonate. A young woman with a prosthetic heart valve was successfully managed throughout pregnancy with the aid of dipyridamole and delivered a healthy infant.— R. Ahmad *et al.* (letter), *Lancet*, 1976, *2*, 1414. See also Y. Biale *et al.* (letter), *Lancet*, 1977, *1*, 907.

Absorption and Fate. Dipyridamole is readily absorbed from the gastro-intestinal tract. It is concentrated in the liver and is mainly excreted in the faeces. Excretion may be delayed by reabsorption. A small amount is excreted in the urine as glucuronide.

For a study suggesting that blood-dipyridamole concentrations below 3.5 µmol per litre may not be effective in suppressing platelet function, see under Cardiac Disorders, below.

Uses. Dipyridamole has antithrombotic activity and is used in conditions where modification of platelet function may be beneficial. For this purpose the usual dose is 100 mg four times daily before food increased if necessary, to 600 mg daily.
It has also been used as a vasodilator in the long-term management of chronic angina pectoris in usual doses of 50 mg thrice daily. It has also been given by slow intravenous injection in a dose of 10 to 20 mg twice or thrice daily.

Action. Evidence to suggest that the antithrombotic activity of phosphodiesterase inhibitors, such as dipyridamole, depend upon the activation of platelet adenylcyclase by potentiation of endogenous prostacyclin.— S. Moncada and R. Korbut, *Lancet*, 1978, *1*, 1286. Comments.— D. F. Horrobin *et al.* (letter), *ibid.*, *2*, 270; A. K. Pedersen (letter), *ibid.* *In vitro* studies pointing to an effect of dipyridamole on prostaglandin metabolism in platelets, which might provide an additional explanation of its activity as an inhibitor of platelet function.— L. C. Best *et al.* (letter), *ibid.*, 846. *In vitro* tests indicating that inhibition of thromboxane synthetase cannot explain the antithrombotic effects of dipyridamole.— S. Moncada *et al.* (letter), *ibid.*, 1257. Findings indicating that dipyridamole has an inhibitory effect on platelet aggregation, dependent on albumin but independent of prostacyclin and thromboxane.— K. A. Jørgensen and E. Stoffersen (letter), *ibid.*, 1258. Data suggesting that the most important mechanism of action of dipyridamole might be enhancement of the effects of prostacyclin.— G. Di Minno *et al.* (letter), *ibid*

In a study involving 10 healthy subjects dipyridamole 8 µg per kg body-weight per minute, infused for 2 hours, induced an increase of prostacyclin release, probably by a direct effect on the metabolic pathways of arachidonic acid.— G. Masotti *et al.* (letter), *Lancet*, 1979, *1*, 1412. A study in 4 healthy subjects indicating that dipyridamole ingestion appeared to diminish rather than enhance the effect of prostacyclin (and other prostaglandins) as platelet-aggregate inhibitors in human platelet-rich plasma. These findings do not support the hypothesis that the antithrombotic action of dipyridamole is caused by enhancement of platelet aggregate inhibition by 'circulating' prostacyclin.— G. Di Minno *et al.* (letter), *ibid.*, 1979, *2*, 701. In 10 juvenile-onset, insulin-dependent diabetics, dipyridamole significantly decreased their raised plasma concentrations of β-thromboglobulin without affecting metabolic control. This might be based on enhancement or release of prostacyclin.— G. Schernthaner *et al.* (letter), *ibid.*, 748.

Cardiac disorders. For the role of dipyridamole in the prevention of myocardial infarction, see Aspirin, p.242.

Cardiac surgery. Dipyridamole was considered to reduce the incidence of thrombo-embolic episodes during the year following heart-valve replacement. In a study in 70 patients, 27 were given dipyridamole 400 mg daily and 36 a placebo, starting 10 to 14 days after operation. All patients received warfarin sodium. There were 11 thrombo-embolic episodes among the patients receiving placebos but none among those continuously taking

Precautions: Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

PREGNANCY: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to ten times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclacillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cyclacillin is administered to a nursing woman.

Adverse Reactions: The oral administration of cyclacillin is generally well-tolerated.

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported with the use of cyclacillin: diarrhea (in approximately 1 out of 20 patients treated), nausea and vomiting (in approximately 1 in 50), and skin rash (in approximately 1 in 60). Isolated instances of headache, dizziness, abdominal pain, vaginitis, and urticaria have been reported. (See WARNINGS.)

Other less-frequent adverse reactions which may occur and that have been reported during therapy with other penicillins are: anemia, thrombocytopenia, thrombocytopenic purpura, leukopenia, neutropenia, and eosinophilia. These reactions are usually reversible on discontinuation of therapy.

As with other semisynthetic penicillins, SGOT elevations have been reported.

Dosage and Administration:

[See table on preceding page].

Patients with Renal Failure

Based on a dosage of 500 mg q.i.d., the following adjustment in dosage interval is recommended:

Patients with a creatinine clearance of > 50 ml/min need no dosage interval adjustment.

Patients with a creatinine clearance of 30–50 ml/min receive full doses every 12 hours.

Patients with a creatinine clearance of between 15–30 ml/min should receive full doses every 18 hours.

Patients with a creatinine clearance of between 10–15 ml/min should receive full doses every 24 hours.

In patients with a creatinine clearance of ≤ 10 ml/min or serum creatinine values of ≥ 10 mg%, serum cyclacillin levels are recommended to determine both subsequent dosage and frequency.

How Supplied: Cyclapen-W® (cyclacillin) tablets are available in the following strengths:

250 mg, NDC 0008-0614, yellow capsule-shaped scored tablet embossed with "WYETH" and "614", supplied in bottles of 100 tablets.

500 mg, NDC 0008-0615, yellow capsule-shaped scored tablet embossed with "WYETH" and "615", supplied in bottles of 100 tablets.

The appearance of Cyclapen-W tablets is a registered trademark of Wyeth Laboratories.

Keep bottles tightly closed.

Dispense in tight containers.

Cyclapen-W (cyclacillin) for oral suspension is available in the following strengths:

125 mg per 5 ml, NDC 0008-0599, white to pinkish-white powder supplied in bottles to make 100, 150, and 200 ml of suspension.

250 mg per 5 ml, NDC 0008-0600, white to pinkish-white powder supplied in bottles to make 100, 150, and 200 ml of suspension.

Shake well before using—Keep tightly closed.

After reconstituting, as directed on the package label, store under refrigeration. Discard any unused portion after 14 days.

References:

1. BAUER, A.W., KIRBY, W.M.M., SHERRIS, J.C. and TURCK, M.; Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol. 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-2

2. ...onal Committee for Laboratory Standards; Approved Standard-2; Performance Standards for Antimicrobial Disc Susceptibility Tests, 1976.

3. ERICSON, H. M., and SHERRIS, J.C.; Antibiotic Sensitivity Testing Report of an International Collaborative Study, ACTA, Pathol. Microbiol. Scand., Section B:217, 1971.

Shown in Product Identification Section, page 434

CYCLOSPASMOL®

℞

[cīclō'spaz"mōl]

(cyclandelate)

Capsules-Tablets

Composition: Each *blue* and *red* capsule contains 400 mg. of cyclandelate, and each *blue* capsule contains 200 mg. of cyclandelate. Each *orange* tablet contains 100 mg. cyclandelate.

Description: Cyclandelate is a white amorphous powder having a faint menthol-like odor. It is slightly soluble in water and highly soluble in ethyl alcohol and organic solvents. Cyclandelate has the following structural formula: 3,5,5,-trimethylcyclohexyl mandelate.

Actions: CYCLOSPASMOL is an orally acting vasodilator. The activity of this drug, as measured by pharmacological tests against various types of smooth-muscle spasm produced by acetylcholine, histamine, and barium chloride, exceeds that of papaverine, particularly in regard to the neurotropic component produced by the acetylcholine. Cyclandelate is musculotropic, acting directly on vascular smooth muscle, and has no significant adrenergic stimulating or blocking actions.

The drug is not intended to substitute for other appropriate medical or surgical programs in the treatment of peripheral or cerebral vascular disease.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: CYCLOSPASMOL is indicated for adjunctive therapy in intermittent claudication; arteriosclerosis obliterans; thrombophlebitis (to control associated vasospasm and muscular ischemia); nocturnal leg cramps; Raynaud's phenomenon; and for selected cases of ischemic cerebral vascular disease.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: CYCLOSPASMOL is contraindicated in cases of known hypersensitivity to the drug.

Warnings: 1. Cyclandelate should be used with extreme caution in patients with severe obliterative coronary artery or cerebral-vascular disease, since there is a possibility that these diseased areas may be compromised by vasodilatory effects of the drug elsewhere. 2. **Use in Pregnancy:** The safety of cyclandelate for use during pregnancy or lactation has not been established; therefore, it should not be used in pregnant women or in women of childbearing age unless, in the judgment of the physician, its use is deemed absolutely essential to the welfare of the patient. 3. Although no prolongation of bleeding time has been demonstrated in humans in therapeutic dosages, it has been demonstrated in animals at very large doses. Therefore, the hazard of a prolonged bleeding time should be carefully considered when administering cyclandelate to a patient with active bleeding or a bleeding tendency.

Precautions: Since CYCLOSPASMOL (cyclandelate) is a vasodilator, it should be used with caution in patients having glaucoma.

Adverse Reactions: Gastrointestinal distress (pyrosis, pain, and eructation) may occur with CYCLOSPASMOL. These symptoms occur infrequently and are usually mild. Relief can often be obtained by taking the medication with meals or by the concomitant use of antacids.

Mild flush, headache, feeling of weakness, or tachycardia may occur, especially during the first weeks of administration.

Dosage and Administration: It is often advantageous to initiate therapy at higher dosage; e.g.: 1200-1600 mg. per day, given in divided doses before meals and at bedtime. When a clinical response is noted, the dosage can be decreased in 200-mg. decrements until the maintenance dosage is reached. The usual maintenance dosage of CYCLOSPASMOL (cyclandelate) is between 400 and 800 mg. per day given in two to four divided doses.

Although objective signs of therapeutic benefit may be rapid and dramatic, more often, this improvement occurs gradually over weeks of therapy. It is strongly recommended that the patient be educated to the fact that prolonged use may be necessary. Short-term use of CYCLOSPASMOL is rarely beneficial, nor is it likely to be of any permanent value.

How Supplied: 400 mg. blue and red capsules in bottles of 100, and 500; and Clinipak®, Unit Dose Medication, 100 capsules (20 strips of 5). 200 mg. blue capsules in bottles of 100, 500, and 1000; and Clinipak®, Unit Dose Medication, 100 capsules (20 strips of 5); 100 mg. orange tablets in bottles of 100 and 500.

Literature Available: Yes.

[Cir. 3016-2 7/14/80]

Shown in Product Identification Section, page 411

DIPHTHERIA AND TETANUS TOXOIDS

℞

[dif-the're-ah and tet'ah-nus tok'soids]

ADSORBED (PEDIATRIC)

aluminum phosphate adsorbed,

ULTRAFINED®

Description: Antigens adsorbed on aluminum phosphate. Preservative is 0.01% thimerosal (mercury derivative).

How Supplied: Vials of 5 ml.; and 0.5-ml. TUBEX® Sterile Cartridge-Needle Units, packages of 10.

For prescribing information write to Professional Service, Wyeth Laboratories, Box 8299, Philadelphia, PA 19101, or contact your local Wyeth representative.

EQUAGESIC®

℞

[ek"wa-je'zik]

(meprobamate with aspirin)

Description: Each tablet of Equagesic contains 200 mg meprobamate and 325 mg aspirin.

Actions: Meprobamate is a carbamate derivative which has been shown (in animal and/or human studies) to have effects at multiple sites in the central nervous system, including the thalamus and limbic system.

Aspirin, acetylsalicylic acid, is a nonnarcotic analgesic with antipyretic and antiinflammatory properties.

Indications: As an adjunct in the short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease. Clinical trials have demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone.

The effectiveness of Equagesic in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindications:

ASPIRIN:

Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE:

Acute intermittent porphyria and allergic or idiosyncratic reactions to meprobamate or related compounds, such as carisoprodol, mebutamate, or carbromal.

Warnings:

ASPIRIN:

Salicylates should be used with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or in those on anticoagulant therapy.

In rare instances, the use of aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE:

DRUG DEPENDENCE: Physical dependence, psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually, greater-than-recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, careful supervision of dose and amounts prescribed is advised, as well as avoidance of prolonged administration, especially for alcoholics and other patients with a known propensity for taking excessive quantities of drugs.

Sudden withdrawal of the drug after prolonged and excessive use may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia, or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinosis, and, rarely, convulsive seizures. Such seizures are more likely to occur in persons with central-nervous-system damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation of meprobamate; symptoms usually cease within the next 12- to 48-hour period.

When excessive dosage has continued for weeks or months, dosage should be reduced gradually over a period of 1 to 2 weeks rather than abruptly stopped. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Patients should be warned that meprobamate may impair the mental or physical abilities required for performance of potentially hazardous tasks, such as driving or operating machinery.

ADDITIVE EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, appropriate caution should be exercised with patients who take more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION

An increased risk of congenital malformations associated with the use of minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during

Continued on next page

Precautions: Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

PREGNANCY: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to ten times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclacillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cyclacillin is administered to a nursing woman.

Adverse Reactions: The oral administration of cyclacillin is generally well-tolerated.

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported with the use of cyclacillin: diarrhea (in approximately 1 out of 20 patients treated), nausea and vomiting (in approximately 1 in 50), and skin rash (in approximately 1 in 60). Isolated instances of headache, dizziness, abdominal pain, vaginitis, and urticaria have been reported. (See WARNINGS.)

Other less-frequent adverse reactions which may occur and that have been reported during therapy with other penicillins are: anemia, thrombocytopenia, thrombocytopenic purpura, leukopenia, neutropenia, and eosinophilia. These reactions are usually reversible on discontinuation of therapy.

As with other semisynthetic penicillins, SGOT elevations have been reported.

Dosage and Administration:

[See table on preceding page].

Patients with Renal Failure

Based on a dosage of 500 mg q.i.d., the following adjustment in dosage interval is recommended:

Patients with a creatinine clearance of > 50 ml/min need no dosage interval adjustment.

Patients with a creatinine clearance of 30–50 ml/min should receive full doses every 12 hours.

Patients with a creatinine clearance of between 15–30 ml/min should receive full doses every 18 hours.

Patients with a creatinine clearance of between 10–15 ml/min should receive full doses every 24 hours.

In patients with a creatinine clearance of ≤ 10 ml/min or serum creatinine values of ≥ 10 mg%, serum cyclacillin levels are recommended to determine both subsequent dosage and frequency.

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500 mg, NDC 0008-0615, yellow capsule-shaped scored tablet embossed with "WYETH" and "615", supplied in bottles of 100 tablets.

The appearance of Cyclapen-W tablets is a registered trademark of Wyeth Laboratories.

Keep bottles tightly closed.

Dispense in tight containers.

Cyclapen-W (cyclacillin) for oral suspension is available in the following strengths:

125 mg per 5 ml, NDC 0008-0599, white to pinkish-white powder supplied in bottles to make 100, 150, and 200 ml of suspension.

250 mg per 5 ml, NDC 0008-0600, white to pinkish-white powder supplied in bottles to make 100, 150, and 200 ml of suspension.

Shake well before using—Keep tightly closed.

After reconstituting, as directed on the package label, store under refrigeration. Discard any unused portion after 14 days.

References:

1. BAUER, A.W., KIRBY, W.M.M., SHERRIS, J.C. and TURCK, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol. 45:493, 1966. Standardized Susceptibility Test, FEDERAL REGISTER 37:20527-372.

National Committee for Laboratory Standards: Approved Standard-2; Performance Standards for Antimicrobial Disc Susceptibility Tests, 1976.

3. ERICSON, H. M., and SHERRIS, J.C.: Antibiotic Sensitivity Testing Report of an International Collaborative Study, ACTA, Pathol. Microbiol. Scand., Section B:217, 1971.

Shown in Product Identification Section, page 434

CYCLOSPASMOL®

B

[cīclō'spas"mól]

(cyclandelate)

Capsules-Tablets

Composition: Each *blue* and *red* capsule contains 400 mg. of cyclandelate, and each *blue* capsule contains 200 mg. of cyclandelate. Each *orange* tablet contains 100 mg. cyclandelate.

Description: Cyclandelate is a white amorphous powder having a faint menthol-like odor. It is slightly soluble in water and highly soluble in ethyl alcohol and organic solvents. Cyclandelate has the following structural formula: 3,5,5,-trimethylcyclohexyl mandelate.

Actions: CYCLOSPASMOL is an orally acting vasodilator. The activity of this drug, as measured by pharmacological tests against various types of smooth-muscle spasm produced by acetylcholine, histamine, and barium chloride, exceeds that of papaverine, particularly in regard to the neurotropic component produced by the acetylcholine. Cyclandelate is musculotropic, acting directly on vascular smooth muscle, and has no significant adrenergic stimulating or blocking actions.

The drug is not intended to substitute for other appropriate medical or surgical programs in the treatment of peripheral or cerebral vascular disease.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: CYCLOSPASMOL is indicated for adjunctive therapy in intermittent claudication; arteriosclerosis obliterans; thrombophlebitis (to control associated vasospasm and muscular ischemia); nocturnal leg cramps; Raynaud's phenomenon; and for selected cases of ischemic cerebral vascular disease.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: CYCLOSPASMOL is contraindicated in cases of known hypersensitivity to the drug.

Warnings: 1. Cyclandelate should be used with extreme caution in patients with severe obliterative coronary artery or cerebral-vascular disease, since there is a possibility that these diseased areas may be compromised by vasodilatory effects of the drug elsewhere. 2. **Use in Pregnancy:** The safety of cyclandelate for use during pregnancy or lactation has not been established; therefore, it should not be used in pregnant women or in women of childbearing age unless, in the judgment of the physician, its use is deemed absolutely essential to the welfare of the patient. 3. Although no prolongation of bleeding time has been demonstrated in humans in therapeutic dosages, it has been demonstrated in animals at very large doses. Therefore, the hazard of a prolonged bleeding time should be carefully considered when administering cyclandelate to a patient with active bleeding or a bleeding tendency.

Precautions: Since CYCLOSPASMOL (cyclandelate) is a vasodilator, it should be used with caution in patients having glaucoma.

Adverse Reactions: Gastrointestinal distress (pyrosis, pain, and eructation) may occur with CYCLOSPASMOL. These symptoms occur infrequently and are usually mild. Relief can often be obtained by taking the medication with meals or by the concomitant use of antacids.

Mild flush, headache, feeling of weakness, or tachycardia may occur, especially during the first weeks of administration.

Dosage and Administration: It is often advantageous to initiate therapy at higher dosage; e.g.: 1200-1600 mg. per day, given in divided doses before meals and at bedtime. When a clinical response is noted, the dosage can be decreased in 200-mg. decrements until the maintenance dosage is reached. The usual maintenance dosage of CYCLOSPASMOL (cyclandelate) is between 400 and 800 mg. per day given in two to four divided doses.

Although objective signs of therapeutic benefit may be rapid and dramatic, more often, this improvement occurs gradually over weeks of therapy. It is strongly recommended that the patient be educated to the fact that prolonged use may be necessary. Short-term use of CYCLOSPASMOL is rarely beneficial, nor is it likely to be of any permanent value.

How Supplied: 400 mg. blue and red capsules in bottles of 100, and 500; and Clinipak®, Unit Dose Medication, 100 capsules (20 strips of 5). 200 mg. blue capsules in bottles of 100, 500, and 1000; and Clinipak®, Unit Dose Medication, 100 capsules (20 strips of 5); 100 mg. orange tablets in bottles of 100 and 500.

Literature Available: Yes.

[Cir. 3016-2 7/14/80]

Shown in Product Identification Section, page 411

DIPTHERIA AND TETANUS TOXOIDS

B

[dif-the're-ah and tet'ah-nus tok'soids]

ADSORBED (PEDIATRIC)

aluminum phosphate adsorbed,

ULTRAFINED®

Description: Antigens adsorbed on aluminum phosphate. Preservative is 0.01% thimerosal (mercury derivative).

How Supplied: Vials of 5 mL; and 0.5-mL. TUBEX® Sterile Cartridge-Needle Units, packages of 10.

For prescribing information write to Professional Service, Wyeth Laboratories, Box 8299, Philadelphia, PA 19101, or contact your local Wyeth representative.

EQUAGESIC®

℄ B

[ek"wa-je'zik]

(meprobamate with aspirin)

Description: Each tablet of Equagesic contains 200 mg meprobamate and 325 mg aspirin.

Actions: Meprobamate is a carbamate derivative which has been shown (in animal and/or human studies) to have effects at multiple sites in the central nervous system, including the thalamus and limbic system.

Aspirin, acetylsalicylic acid, is a nonnarcotic analgesic with antipyretic and antiinflammatory properties.

Indications: As an adjunct in the short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease. Clinical trials have demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone.

The effectiveness of Equagesic in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindications:

ASPIRIN:

Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE:

Acute intermittent porphyria and allergic or idiosyncratic reactions to meprobamate or related compounds, such as carisoprodol, mebutamate, or carbromal.

Warnings:

ASPIRIN:

Salicylates should be used with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or in those on anticoagulant therapy.

In rare instances, the use of aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE:

DRUG DEPENDENCE: Physical dependence, psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually, greater-than-recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, careful supervision of dose and amounts prescribed is advised, as well as avoidance of prolonged administration, especially for alcoholics and other patients with a known propensity for taking excessive quantities of drugs.

Sudden withdrawal of the drug after prolonged and excessive use may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia, or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinosis, and, rarely, convulsive seizures. Such seizures are more likely to occur in persons with central-nervous-system damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation of meprobamate; symptoms usually cease within the next 12- to 48-hour period.

When excessive dosage has continued for weeks or months, dosage should be reduced gradually over a period of 1 to 2 weeks rather than abruptly stopped. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Patients should be warned that meprobamate may impair the mental or physical abilities required for performance of potentially hazardous tasks, such as driving or operating machinery.

ADDITIVE EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, appropriate caution should be exercised with patients who take more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION

An increased risk of congenital malformations associated with the use of minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during

Continued on next page

Nylidrin Hydrochloride Tablets *(U.S.P.)*. Tablets containing buphenine hydrochloride. Store in airtight containers.

Proprietary Names

Arlibide *(US Vitamin, Arg.)*; Arlidin *(USV, Canad.; USV Pharmaceutical Corp., USA)*; Bufedon *(Cedona, Neth.)*; Dilatol *(Tropon, Ger.)*; Dilydrin *(Medichemie, Switz.)*; Opino *(Bayropharm, Ital.)*; Penitardon *(Woelm, Ger.)*; Pervadil *(ICN, Canad.)*; Tocodrin *(Medichemie, Switz.)*.

Buphenine hydrochloride was formerly marketed in Great Britain under the proprietary name Perdilatal Forte *(Smith & Nephew Pharmaceuticals)*.

9215-s

Butalamine Hydrochloride. LA 1221. *NN*-Dibutyl-*N'*-(3-phenyl-1,2,4-oxadiazol-5-yl)ethylenediamine hydrochloride.

$C_{18}H_{28}N_4O.HCl = 352.9$.

CAS — 22131-35-7 (butalamine); 56974-46-0 (hydrochloride).

A white crystalline powder. M.p. 135° to 141°. **Soluble** 1 in 7 of water, 1 in 10 of alcohol, and 1 in 2.5 of chloroform.

Butalamine hydrochloride is a vasodilator which has been given in the treatment of peripheral vascular disorders.

Proprietary Names

Adrevil *(Zyma, Ger.)*; Hemotrope *(Andromaco, Arg.)*; Surem *(CEPA, Spain)*; Surheme *(Aron, Fr.; Spemsa, Ital.)*.

9216-w

Butoxyethyl Nicotinate. 2-Butoxyethyl nicotinate.

$C_{12}H_{17}NO_3 = 223.3$.

CAS — 13912-80-6.

Butoxyethyl nicotinate is a topical vasodilator used, in a concentration of 2.5%, in rubefacient ointments.

Proprietary Preparations

See under Methyl Nicotinate, p.1626.

9217-c

Cetiedil Citrate. 2-(Perhydroazepin-1-yl)ethyl α-cyclohexyl-α-(3-thienyl)acetate dihydrogen citrate monohydrate.

$C_{20}H_{31}NO_2S.C_6H_8O_7.H_2O = 559.7$.

CAS — 14176-10-4 (cetiedil); 16286-69-4 (citrate, anhydrous).

Cetiedil citrate is a vasodilator which has been given in the treatment of peripheral vascular disorders.

After intravenous injection of radioactively labelled cetiedil, 50% of the dose was metabolised within 5 minutes, and after 1 hour only labelled metabolites were recovered from the urine. Cetiedil was also shown to be rapidly metabolised after administration by mouth, and after first pass through the liver only metabolites would enter the general circulation. It was concluded that the metabolites of cetiedil were active as inhibition of saliva secretion persisted when cetiedil could no longer be detected in plasma.— A. M. Soeterboek *et al., Eur. J. clin. Pharmac.*, 1977, *12*, 205.

Asthma. References to bronchodilator activity of cetiedil citrate: J. Orehek *et al., Nouv. Presse méd.*, 1976, *5*, 1577; Y. W. Cho *et al., Int. J. clin. Pharmac. Biopharm.*, 1978, *16*, 402.

Peripheral vascular disorders. An evaluation of cetiedil, administered intravenously, intramuscularly, or by mouth, in the treatment of peripheral vascular disorders.— R. Barbe *et al., Clin. Trials J.*, 1980, *17*, 20.

Proprietary Names

Stratene *(Innothéra, Fr.; Sigmatau, Ital.)*.

9218-l

Chromonar Hydrochloride. Carbocromen Hydrochloride; A27053; AG 3; Cassella 4489. Ethyl 3-(2-diethylaminoethyl)-4-methylcoumarin-7-yloxyacetate hydrochloride.

$C_{20}H_{27}NO_5.HCl = 397.9$.

CAS — 804-10-4 (chromonar); 655-35-6 (hydrochloride).

A white crystalline powder with a bitter taste. M.p. about 159°. **Soluble** in water, alcohol, and chloroform.

Chromonar hydrochloride is a vasodilator which has been used in the prophylaxis of angina pectoris.

For reports of pharmacological studies, see R. E. Nitz and E. Potzsch, *Arzneimittel-Forsch.*, 1963, *13*, 243; W. Lochner and H. Hirche, *ibid.*, 251; H. J. Bretschneider *et al., ibid.*, 255.

Absorption, blood concentrations, and excretion of chromonar.— Y. C. Martin and R. -G. Wiegand, *J. pharm. Sci.*, 1970, *59*, 1313.

Cardiac disorders. A multicentre double-blind crossover study of 187 patients with angina pectoris who received chromonar for 8 weeks (79 patients) or 12 weeks (108 patients) at a dosage of 150 mg thrice daily (73 patients) or 225 mg thrice daily (114 patients) demonstrated significant prevention of anginal attacks by the lower dose, and improvement in attack-rate and glyceryl trinitrate requirement by the higher dose although the higher dose failed to show any advantage over placebo when the glyceryl trinitrate requirement was considered alone.— R. J. Bing *et al., Clin. Pharmac. Ther.*, 1974, *16*, 4. See also H. Bell *et al., ibid.*, 1968, *9*, 40.

Further references: G. Faucon *et al., Thérapie*, 1975, *30*, 185; E. Schraven, *Arzneimittel-Forsch.*, 1976, *26*, 197; E. Schraven *et al., ibid.*, 200; R. Sirbulescu *et al., ibid.*, 204; N. N. Kipsidze and G. M. Kikava, *ibid.*, 1976, *26*, 882.

Proprietary Names

Antiangor *(ISM, Ital.)*; Cardiocap *(Fidia, Ital.)*; Cromene *(Scharper, Ital.)*; Intensain *(Cassella-Riedel, Belg.; Diamant, Fr.; Cassella-Riedel, Ger.; Pierrel, Ital.; Jap.;Boehringer Mannheim, S.Afr.; Albert-Farma, Spain; Cassella-Riedel, Switz.)*; Intensacrom *(Albert-Farma, Spain)*.

9219-y

Cinepazet Maleate. Cinepazic Acid Ethyl Ester Maleate. Ethyl 4-(3,4,5-trimethoxycinnamoyl)piperazin-1-ylacetate hydrogen maleate.

$C_{20}H_{28}N_2O_6.C_4H_4O_4 = 508.5$.

CAS — 23887-41-4 (cinepazet); 50679-07-7 (maleate).

A white powder. M.p. 130°.

Cinepazet maleate is a vasodilator which has been used in the treatment of angina pectoris.

Absorption and fate of cinepazet in man. Most of a dose given by mouth was eliminated within 24 hours, 60% being excreted in the urine. The major metabolite was cinepazic acid.— L. F. Chasseaud *et al., Arzneimittel-Forsch.*, 1972, *22*, 2003.

Proprietary Names

Vascoril *(Delalande, Belg.; Delalande, Fr.; Delalande, Ital.; Delalande, Switz.)*.

9220-g

Cinepazide Maleate. 1-(Pyrrolidin-1-ylcarbonylmethyl)-4-(3,4,5-trimethoxycinnamoyl)piperazine hydrogen maleate.

$C_{22}H_{31}N_3O_5.C_4H_4O_4 = 533.6$.

CAS — 23887-46-9 (cinepazide); 26328-04-1 (maleate).

Cinepazide maleate is a vasodilator which has been given in peripheral and cerebral vascular disorders and in coronary insufficiency.

Pharmacology in animals.— B. Pourrias *et al., Thérapie*, 1974, *29*, 29 and 43.

Proprietary Names

Vasodistal *(Delalande, Fr.; Delalande, Ital.; Delalande, Switz.)*.

9221-q

Cloridarol. Clobenfurol. α-(Benzofuran-2-yl)-α-(4-chlorophenyl)methanol.

$C_{15}H_{11}ClO_2 = 258.7$.

CAS — 3611-72-1.

A white odourless crystalline powder. M.p. about 48°.

Cloridarol has been given in the prevention and treatment of coronary insufficiency.

Proprietary Names

Cordium *(Massone, Arg.)*; Menacor *(Menarini, Ital.)*; Menoxicor *(Menarini, Spain)*.

9222-p

Cyclandelate. BS 572. 3,3,5-Trimethylcyclohexyl mandelate.

$C_{17}H_{24}O_3 = 276.4$.

CAS — 456-59-7.

A white to off-white amorphous powder with a slight menthol-like odour and a bitter taste. M.p. below 60°. On storage it may sublime into a crystalline form resembling cotton wool.

Practically **insoluble** in water; soluble 1 in about 1 of alcohol and 1 in about 2 of light petroleum; very soluble in ether and other common organic solvents. **Store** in a cool place in airtight containers. Protect from light.

Adverse Effects. Nausea, gastro-intestinal distress, or flushing may follow high doses of cyclandelate.

Other adverse effects reported include tingling and headache.

Toxicity of cyclandelate was low, though with large doses there might be flushing, tingling, nausea, or headache.— T. Winsor and C. Hyman, *Clin. Pharmac. Ther.*, 1961, *2*, 652.

Treatment of Adverse Effects. In severe overdosage the stomach should be emptied by aspiration and lavage. If necessary the circulation should be maintained with infusions of suitable electrolytes, and if necessary by vasopressors.

Precautions. Cyclandelate is contra-indicated in the acute phase of a cerebrovascular accident.

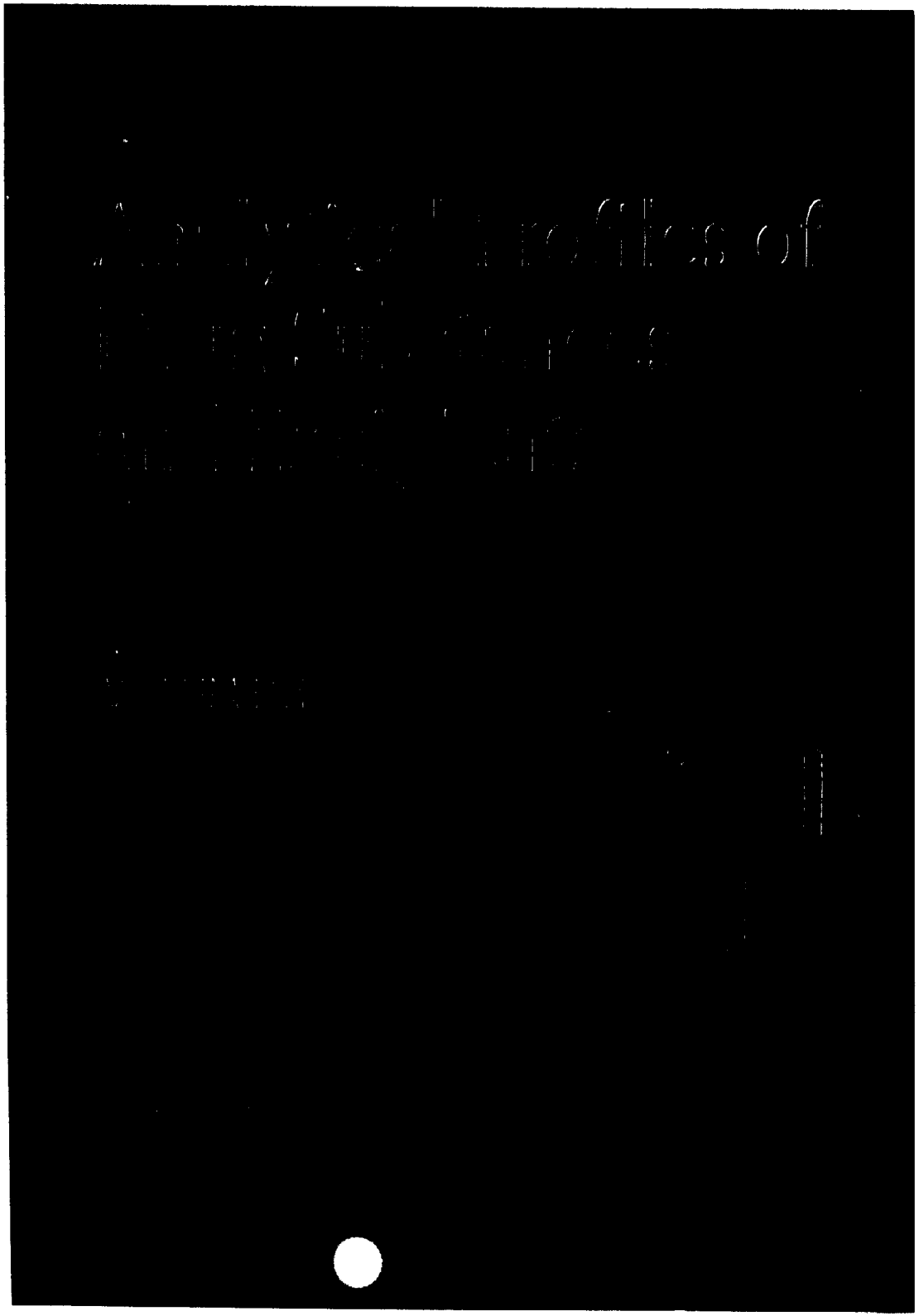
Uses. Cyclandelate is a vasodilator used in the treatment of cerebrovascular and peripheral vascular disorders. It is given in a dosage of 1.6 g daily in divided doses.

Action. *Animal* studies into the mode of action of cyclandelate: A. B. H. Funcke *et al., Curr. med. Res. Opinion*, 1974, *2*, 37 (brain glucose uptake); G. van Hell, *Curr. med. Res. Opinion*, 1974, *2*, 211 (collateral vessel formation).

Cerebrovascular disease. Several double-blind studies of cyclandelate have shown improvement in orientation, disturbed behaviour, and vocabulary without improvement in self-care, recent memory, or mood. Nevertheless, the overall results are inconsistent, and improvements in clinical and psychological tests are not always matched by useful changes in the activities of daily living.— *Br. med. J.*, 1978, *2*, 348. See also *Drug & Ther. Bull.*, 1975, *13*, 85. Further reviews: *Med. Lett.*, 1976, *18*, 38; P. Cook and I. James, *New Engl. J. Med.*, 1981, *305*, 1508 and 1560.

Individual reports and studies on the role of cyclandelate in cerebrovascular disease: J. Young *et al., Br. J. Psychiat.*, 1974, *124*, 177; P. Hall, *J. Am. Geriat. Soc.*, 1976, *24*, 41; G. Davies *et al., Age and Ageing*, 1977, *6*, 156; D. B. Rao *et al., J. Am. Geriat. Soc.*, 1977, *25*, 548; R. Brasseur, *Angiology*, 1978, *29*, 121; B. Capote and N. Parikh, *J. Am. Geriat. Soc.*, 1978, *26*, 360; G. F. A. Harding *et al., Angiology*, 1978, *29*, 139; L. Sourander and C. B. Blakemore, *ibid.*, 133.

Diabetic retinopathy. In a double-blind randomised study deterioration of the blood-retinal barrier was assessed in 22 diabetic patients, without retinal involvement, by vitreous fluorophotometry after the injection of fluorescein. It was considered that deterioration of the blood-retinal barrier, an early sign of diabetic retinopathy, was delayed in the third month in those patients given cyclandelate 400 mg four times daily for 3 months. Long-term studies were considered to be indicated.— J. G. Cunha-Vaz *et al., Br. J. Ophthal.*, 1977,



CYCLANDELATE

Charles M. Shearer

Wyeth-Ayerst Research

Rouses Point, NY 12979

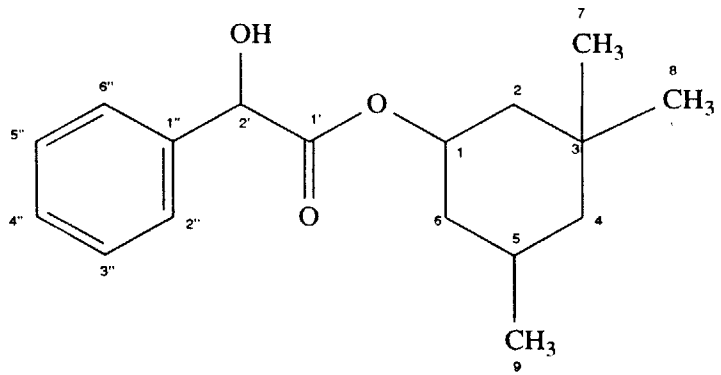
1. Description

1.1 Name, Formula, Molecular Weight

The name used by Chemical Abstracts for cyclandelate is α-hydroxybenzeneacetic acid, 3,3,5-trimethylcyclohexyl ester. It is also called mandelic acid, 3,3,5-trimethylcyclohexyl ester; 3,3,5-trimethylcyclohexyl mandelate; 3,3,5-trimethylcyclohexyl amygdalate; and 3,3,5-trimethylcyclohexanol α-phenyl-α-hydroxyacetate Trade names include, Cyclospasmol, Natil, Novodil, Perebral, and Spasmocyclon (1). The Chemical Abstracts number is 456-59-7.

1.2 Appearance, Color and Odor

Cyclandelate is a white to off-white amorphous powder with a slight menthol-like odor.



$C_{17}H_{24}O_3$ M. W. 276.36

2. Synthesis

Trimethylcyclohexyl mandelate was first synthesized by reacting dl-mandelic acid with 3,3,5-trimethylcyclohexanol (consisting of cis and trans isomers) (2,3,4). Cyclandelate is now synthesized using only the low melting (cis) isomer of 3,3,5-trimethylcyclohexanol (5,6). Esters of mandelic acid with the higher melting 3,3,5-trimethylcyclohexanol are twice as toxic as those made with the low melting isomer (7). The major side reaction product, trimethylcyclohexylphenyl glyoxalate, can be removed during the synthesis by treating the crude cyclandelate with aqueous sodium borohydride (8) or zinc and hydrochloric acid (9).

This synthesis, using only the cis isomer, results in four isomers as described in the next section.

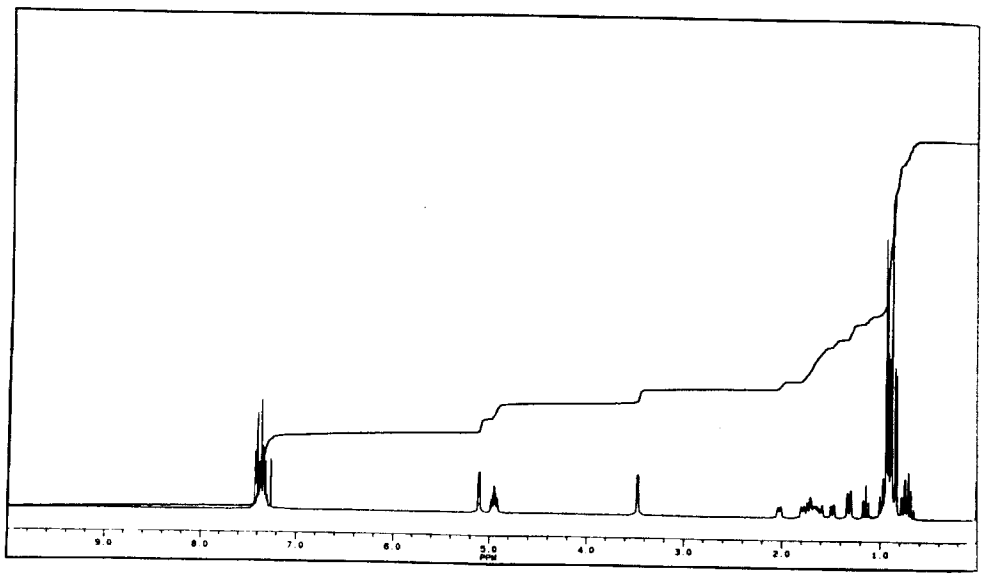


Figure 1 - Proton NMR Spectrum of Cyclandelate (Wyeth-Ayerst Reference Standard No. 1361) in deuterated chloroform

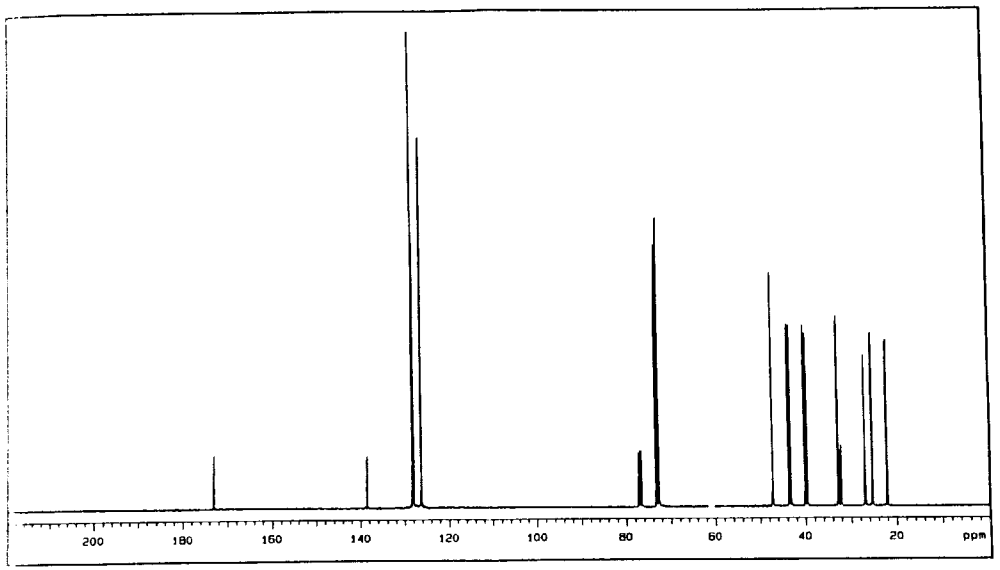


Figure 2 - Carbon -13 NMR Spectrum of Cyclandelate (Wyeth-Ayerst Reference Standard No. 1361) in deuterated chloroform

3. Physical Properties

3.1 Nuclear Magnetic Resonance Spectra

The four isomers which make up cyclandelate arise in the synthesis from the reaction of dl-mandelic acid with cis-3,3,5-trimethylcyclohexanol and are described in Table I (taken from Nakamichi (10)).

Table 1
Isomers of Cyclandelate

Isomer	Absolute configuration of mandelic acid moiety[a]	Absolute configuration of cyclohexanol moiety	
		Position 1	Position 5
A	S	R	R
B	R	S	S
C	R	R	R
D	S	S	S

a) The cyclohexanol moieties of A,C and B,D are levorotatory and dextrorotatory, respectively (11). The absolute configuration of (-)-cis-3,3,5-trimethylcyclohexanol is assigned as R on the basis of its chemical correlation with pulegone (12).

The proton NMR sample (Wyeth-Ayerst Reference Standard No. 1361) was dissolved in deuterated chloroform containing tetramethylsilane as an internal standard. The spectrum was obtained (13) on a 400 MHz Bruker spectrometer and is presented as Figure 1. The spectral assignments are listed in Table II. The C-13 NMR sample was also prepared in deuterated chloroform and its spectrum obtained (13) on a 100 MHz Varian spectrometer. The spectrum is presented as Figure 2 and the spectral assignments are listed in Table III. The spectra are in agreement with those of Nakamachi (10).

3.2 Infrared Spectrum

The infrared spectrum of a KBr pellet of cyclandelate (Wyeth-Ayerst Reference Standard No. 1361) was obtained (14) on a Nicolet 20 DX instrument and is presented as Figure 3. The spectral band assignments are given in Table IV.

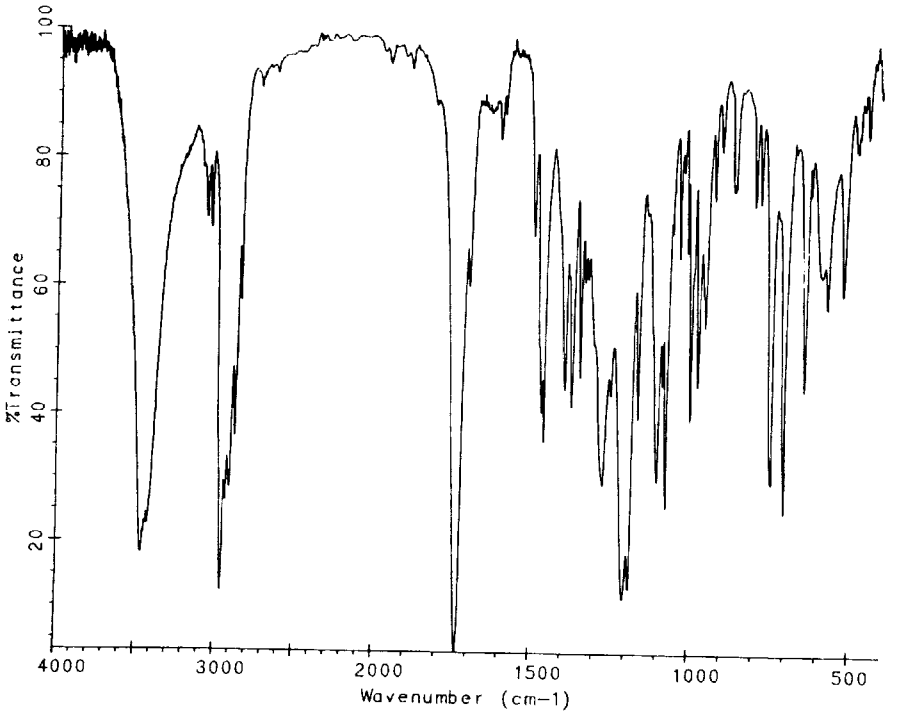


Figure 3 - Infrared Spectrum of Cyclandelate (Wyeth-Ayerst Reference Standard No. 1361) KBr pellet

Table II
Proton NMR Spectral Assignments of Cyclandelate

Chemical Shift (ppm from TMS)	Number of Protons	Assignment
7.4	5	Aromatic C<u>H</u>
5.10 d	1	<u>H</u>-C-OH
4.95 m	1	<u>H</u>-C-OC
3.47 exchangeable	1	<u>H</u>-O
2.1 - 0.6	17	Aliphatic C<u>H</u>, C<u>H</u>$_2$, C<u>H</u>3
0.94 s		gem C<u>H</u>$_3$ (AB pair)
0.88 s		gem C<u>H</u>$_3$ (CD pair)
0.84 d (J = 6)		HC-C<u>H</u>$_3$ (AB pair)
0.91 d (J = 6)		HC-C<u>H</u>$_3$ (CD pair)

Table III
Carbon-13 NMR Spectral Assignments for Cyclandelate

Carbon	ppm	
1	73.3	
2	43.7 (AB)	43.2 (CD)
3	32.2 (AB)	32.1 (CD)
4	47.3	
5	27.0 (AB)	26.9 (CD)
6	39.7 (AB)	40.1 (CD)
7	32.9 (AB)	32.8 (CD)
8	25.4 (AB)	25.3 (CD)
9	22.0 (AB)	22.1 (CD)
1	173.1	
2	72.8	
1	138.6	
2, 6	126.3	
3, 5	128.4	
4	128.1	

Table IV
Infrared Spectral Assignments for Cyclandelate

Wavenumber (Cm^{-1})	Vibration Mode
3460	OH stretch
3100 - 2800	CH stretch
1730	C=O stretch
1212, 1192	C-O-C stretch
730, 695	out-of-plane bending of monosubstituted aromatic

3.3 Ultraviolet Spectrum

The ultraviolet spectrum of cyclandelate (Wyeth-Ayerst Reference Standard No. 1361 recrystallized to remove 0.1% 3,3,5-trimethylcyclohexyl phenylglyoxalate) in USP ethanol is presented as Figure 4. The absorptivities are as follows:

λ max(nm)	a	ε
269	0.57	1575
258	0.73	2020
251	0.59	1630

3.4 Mass Spectrum

The mass spectrum of cyclandelate was obtained (15) by electron impact ionization using a Finnegan MAT 8230 spectrometer and is given as Figure 5. Identification of the pertinent masses is presented in Table V.

Table V
Mass Spectrum Fragmentation Pattern of Cyclandelate

m/e	Species
276	M+
125	$C_9H_{17}^+$
107	$C_6H_5CHOH^+$
83	$CH_2CHCH_2C(CH_3)_2^+$
79	$C_6H_5^+$
69	$CH_2CHCH_2CHCH_3^+$
55	$(CH_3)CCH_2^+$

3.5 Melting Range

Observed (16) melting range (USP Ia) for cyclandelate (Wyeth-Ayerst Reference Standard No. 1361) is 55.0° - 56.5°C.

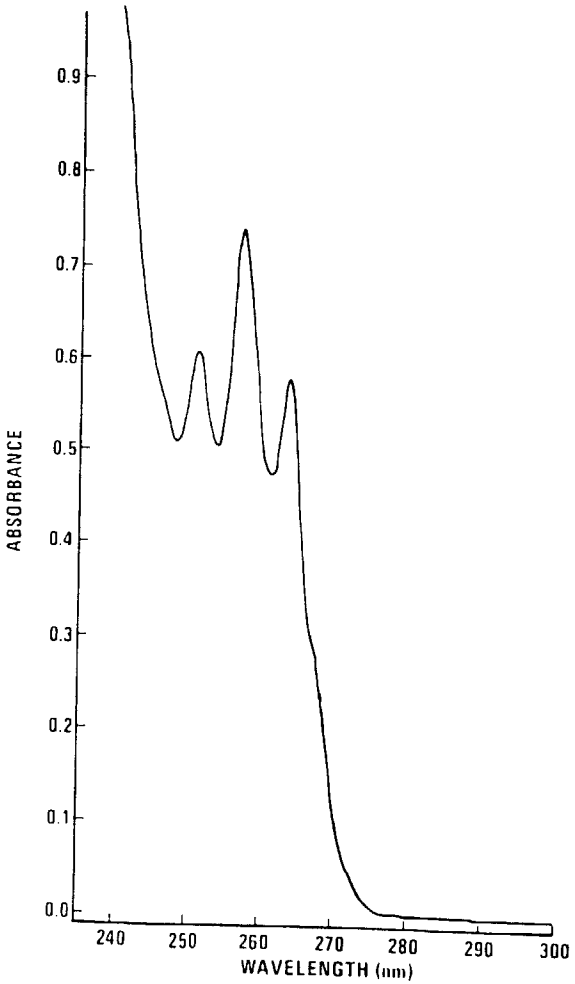


Figure 4 - Ultraviolet Spectrum of Cyclandelate (Wyeth-Ayerst Reference Standard No. 1361) in USP alcohol

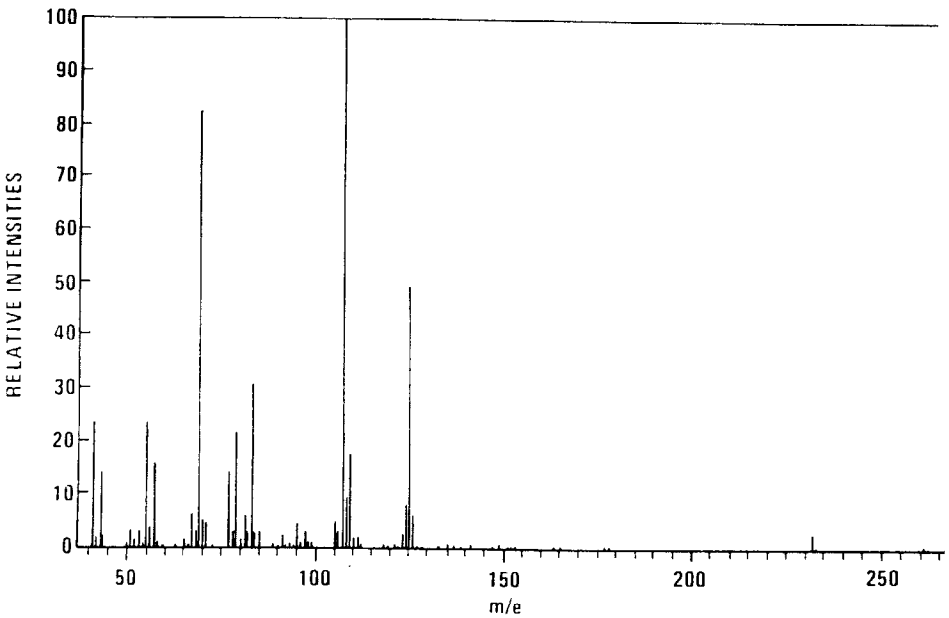


Figure 5 - Mass Spectrum of Cyclandelate (Wyeth-Ayerst Reference Standard No. 1361)

3.6 Differential Scanning Calorimetry

The DSC thermogram (14) for cyclandelate (Wyeth-Ayerst Reference Standard No. 1361) is presented as Figure 6. The thermogram was obtained at a heating rate of 10°C/minute in a nitrogen atmosphere utilizing a Perkin-Elmer DSC-2. The thermogram exhibits no endotherms or exotherms other than that associated with the melt.

3.7 Solubility

The following solubities at room temperature have been observed (16).

USP Classifications:

Solvent	Solubility
Water	insouble
Methanol	very soluble
Acetonitrile	freely soluble
Ethyl acetate	freely soluble
Dimethylformamide	freely soluble
Toluene	freely soluble
Chloroform	very soluble

3.8 Crystal Properties

The X-ray powder diffraction pattern of cyclandelate (Wyeth-Ayerst Reference Standard No. 1361) obtained (14) with a Phillips diffractometer using copper Kα radiation is presented as Figure 7. The calculated "d" spacings are given in Table VI.

Table VI
X-Ray Diffraction Pattern

d	I/I_o	d	I/I_o
19.04	100	4.72	69
11.72	4	4.56	11
9.55	5	4.42	14
7.80	40	3.99	32
7.34	34	3.90	15
6.77	15	3.85	13
6.11	21	3.77	17
5.59	13	3.71	15
5.27	9	3.57	8
4.97	21	2.65	8

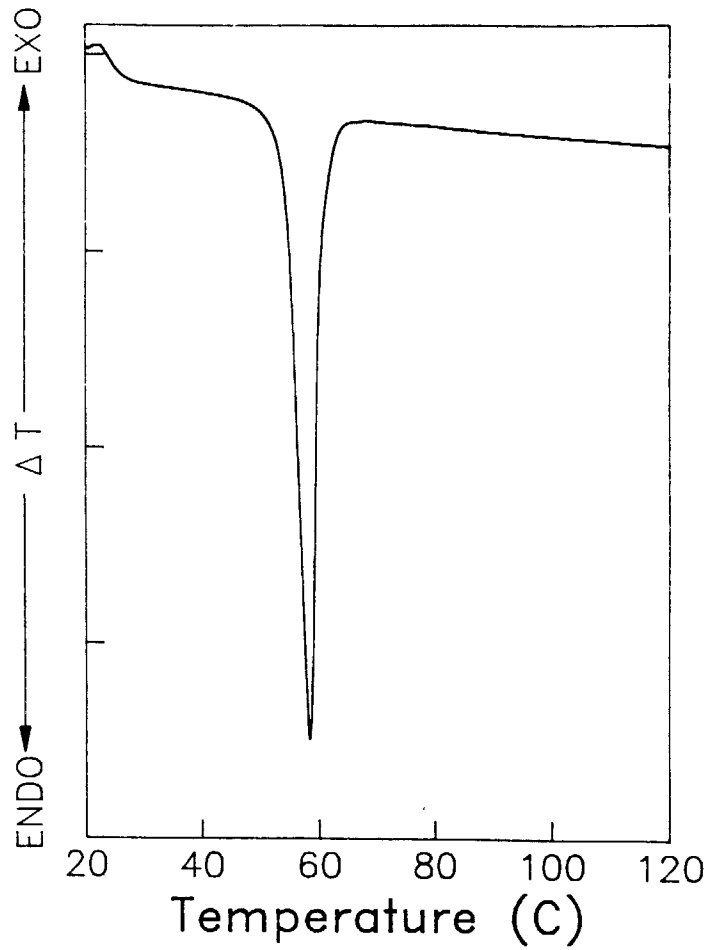


Figure 6 - Differential Scanning Calorimetric Thermogram of Cyclandelate (Wyeth-Ayerst Reference Standard No. 1361)

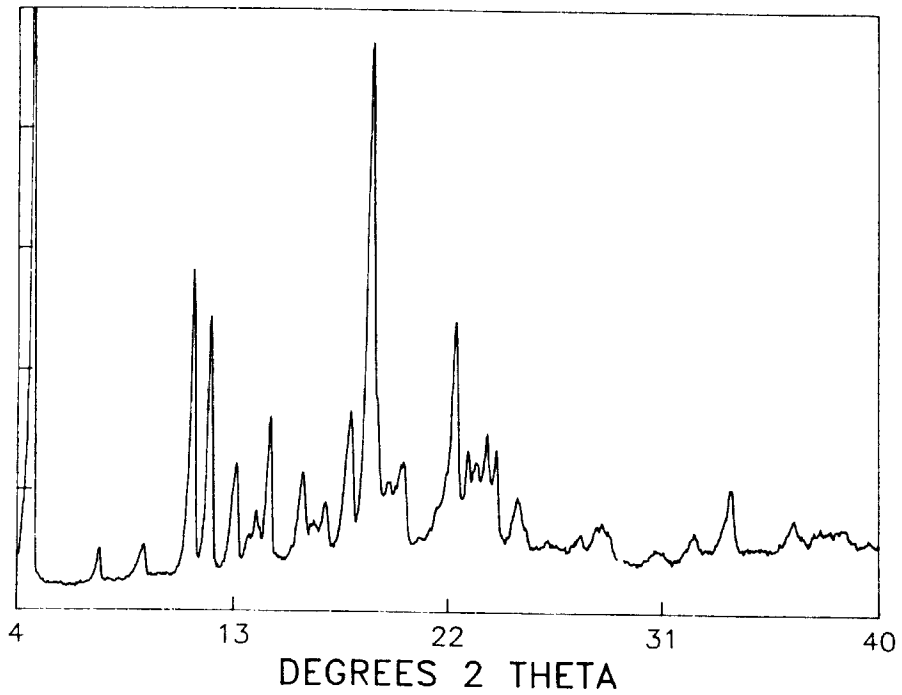


Figure 7 - X-Ray Diffraction Pattern of Cyclandelate (Wyeth-Ayerst Reference Standard No.1361)

4. Stability and Degradation

Cyclandelate can decompose by hydrolysis to mandelic acid and 3,3,5-trimethylcyclohexanol (17). It is oxidized to 3,3,5-trimethylcyclohexyl phenylglyoxalate (18).

A study of the formation of 3,3,5-trimethylcyclohexanol in cyclandelate capsules concluded that less than 5% of the cyclandelate degraded in 66 months at ambient temperatures (17).

5. Metabolism

The metabolites of cyclandelate are mandelic acid, phenylglyoxylic acid and 3,3,5-trimethylcyclohexanol. These are detectable in the urine of rabbits and humans in less than two hours after oral administration (19,20). The ratio of mandelic acid to phenylglyoxylic acid increases with increased dosage (21). Another metabolic study in humans showed that the maximum blood levels of mandelic acid were reached in 0.5 to 1.5 hours after oral dosing (22).

A pharmacokinetic study using tritiated cyclandelate shows that most organ specimens took up the radioactivity rapidly; usually reaching a maximum within one hour. The brain, diaphragm, stomach and vein specimem showed a maximum level at 24 hours. The levels gradually declined in a non-linear manner over 28 days (23).

6. Analysis

6.1 Elemental Analysis

Element	Theory	Found (24)
C	73.88%	73.95%
H	8.75%	8.55%

6.2 Ultraviolet Spectrophotometry

Direct determination of cyclandelate by UV spectrophotometry is not practical since the oxidative degradation product, 3,3,5-trimethylcyclohexyl phenylglyoxalate has about 55 times the absorptivity (25). Spectrophotometric determinations of cyclandelate after hydrolysis to mandelic acid and oxidation to benzaldehyde have been reported (26,27).

6.3 Titrimetry

Cyclandelate can be determined by hydrolyzing the ester in 0.5 N NaOH under reflux for 0.5 hours, then backtitrating the excess base with 0.1 N HCl (28,29).

6.4 Gas Chromatography

Gas chromatography has been used to analyze cyclandelate and to separate it from its degradation products and impurities as well as from other pharmaceuticals. Table VI gives column conditions and other necessary data for the various methods.

Table VI
Gas Chromatography of Cyclandelate

Column	Oven Temperature	Reference
2 m x 4 mm i.d.; 5% QF-1 on Chromosorb W(HP) 100/200 mesh	160°	(30)
6 ft x 1/8 in; 3% QF 1 + 0.5% HiEFF 8BP on GasChrom Q	200°	(31)
25 m x 0.3 mm i.d.; deactivated, coated w/SE-30	125° for 13 min; 3°/min to 180°, hold 1 min.	(32)
30 m x 0.28 mm i.d.; FFAP	170°	(10)
6 ft x 1/4 in i.d.; 15% Dexsil 300 on HP Chromosorb W 80/100 mesh	220°	(33)
1 m x 3.2 mm; Tenax GC 60/80 mesh	140° for 5 min., 20°/min to 240°, 10°/min to 280°	(34)
6 ft x 4 mm i.d.; 2.5% SE30 on 80/100 mesh Chromosorb G	200°	(35)

6.5 High-Performance Liquid Chromatography

An HPLC system consisting of a Microbondapak CN (30 x 0.39 cm.) column, 65% methanol, 35% sodium acetate buffer, adjusted to pH 3.7 as the eluant: and 254 nm UV light for detection has been used (36).

6.6 Thin Layer Chromatography

The following TLC systems have been reported:

Plates	Solvent System	R_f Value	Reference
Silica Gel 254	Benzene		(37)
Silica Gel 254	Hexane 55 Chloroform 45	0.09	(38)
Silica G	Chloroform 4 Acetone 1	0.74	(39)
Silica G	Ethyl Acetate	0.71	(39)

7. Identity

Cyclandelate can be identified amongst many other drugs, poisons and biogenic compounds by gas chromatography (33). Details for this procedure are given in Section 6.4. Several odor and color identification tests are given by Doorenboos and coworkers (28).

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☐ **TITLE:** Cyclandelate in the management of tinnitus: a randomized, placebo-controlled study.
AUTHOR: Hester TO; Theilman G; Green W; Jones RO
AUTHOR AFFILIATION: Division of Otolaryngology-Head and Neck Surgery, University of Kentucky Chandler Medical Center, Lexington 40536-0084, USA.
SOURCE: Otolaryngol Head Neck Surg 1998 Mar;118(3 Pt 1):329-32
NLM CIT. ID: 98186341 (abstract present)

☐ **TITLE:** Functional imaging of headache - first steps in an objective quantitative classification of migraine.
AUTHOR: Sauer S; Schellenberg R; Hofmann HC; Dimpfel W
AUTHOR AFFILIATION: Pro Science Private Research Institute GmbH, med. Forschung und Entwicklung, Kurt-Schumacher-Str. 9, Linden D-35440, Germany.
SOURCE: Eur J Med Res 1997 Sep 29;2(9):367-76
NLM CIT. ID: 97447882 (abstract present)

☐ **TITLE:** Inappropriate medication prescribing for the elderly by office-based physicians.
AUTHOR: Aparasu RR; Fliginger SE
AUTHOR AFFILIATION: College of Pharmacy, South Dakota State University, Brookings 57007 USA. aparasur@mg.sdstate.edu
SOURCE: Ann Pharmacother 1997 Jul-Aug;31(7-8):823-9
NLM CIT. ID: 97363746 (abstract present)

☐ **TITLE:** Pathophysiology and psychopharmacology of dementia--a new study design. 2. Cyclandelate treatment--a placebo-controlled double-blind clinical trial.

AUTHOR:	**Schellenberg R; Todorova A; Wedekind W; Schober F; Dimpfel W**
AUTHOR AFFILIATION:	**Pro Science Private Research Institute GmbH, Linden, Germany.**
SOURCE:	**Neuropsychobiology 1997;35(3):132-42**
NLM CIT. ID:	**97313717 (abstract present)**

☐ **TITLE:** **[Migraine--diagnosis, differential diagnosis and therapy]**

AUTHOR:	**Diener HC**
AUTHOR AFFILIATION:	**Klinik und Poliklinik fur Neurologie, Universitat Essen.**
SOURCE:	**Ther Umsch 1997 Feb;54(2):64-70**
NLM CIT. ID:	**97213591 (abstract present)**

☐ **TITLE:** **Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group.**

AUTHOR:	**Diener HC; Foh M; Iaccarino C; Wessely P; Isler H; Strenge H; Fischer M; Wedekind W; Taneri Z**
AUTHOR AFFILIATION:	**Department of Neurology, Universities of Essen, Germany.**
SOURCE:	**Cephalalgia 1996 Oct;16(6):441-7**
NLM CIT. ID:	**97057925 (abstract present)**

☐ **TITLE:** **Cyclandelate versus propranolol in the prophylaxis of migraine--a double-blind placebo-controlled study.**

AUTHOR:	**Gerber WD; Schellenberg R; Thom M; Haufe C; Bolsche F; Wedekind W; Niederberger U; Soyka D**
AUTHOR AFFILIATION:	**Department of Medical Psychology, University of Kiel, Germany.**
SOURCE:	**Funct Neurol 1995 Jan-Feb;10(1):27-35**
NLM CIT. ID:	**95377668 (abstract present)**

MAIN MESH SUBJECTS:	**Cyclandelate/*THERAPEUTIC USE** **Dementia/*DRUG THERAPY/*PHYSIOPATHOLOGY**
ADDITIONAL MESH SUBJECTS:	**Aged** **Aged, 80 and over** **Double-Blind Method** **Electroencephalography/DRUG EFFECTS** **Female** **Human** **Male** **Middle Age**
PUBLICATION TYPES:	**CLINICAL TRIAL** **JOURNAL ARTICLE** **RANDOMIZED CONTROLLED TRIAL**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**456-59-7 (Cyclandelate)**

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TITLE: Effect of cyclospasmol on early diabetic retinopathy.

AUTHOR: Mota MC; Leite E; Ruas MA; Verjans HL; Blakemore CB; Cunha-Vaz JG

SOURCE: Int Ophthalmol 1987 Feb;10(1):3-9

NLM CIT. ID: 87164769

ABSTRACT: A randomized, double-blind, placebo controlled study to investigate the long-term effect of Cyclospasmol (cyclandelate) on the abnormal permeability of the blood-retinal barrier was performed in 26 patients with insulin-dependent diabetes mellitus for at least 1 year and minimal retinopathy. Cyclospasmol 400 mg or placebo capsules were taken 4 times daily for 12 months by equal numbers in both groups. Each patient underwent a routine ophthalmoscopic examination, retinal fluorescein angiography and quantitative vitreous fluorophotometry to assess the permeability of the blood-retinal barrier just before the trial and following 6 and 12 months of therapy. Laboratory tests for determining blood and urine glucose levels and blood HbA1-levels were also carried out at these assessments. Statistically significant changes in diabetic control, in HbA1-levels or in the frequency of retinal microaneurysms could not be shown in either treatment group during the trial, nor were there any significant differences in these parameters between the two groups. Analysis of fluorophotometric data on fluorescein penetration into the left posterior vitreous demonstrated significant reductions in this parameter during the trial compared to the pretreatment level in Cyclospasmol treated diabetics. These changes in the pretreatment level after 6 and 12 months also differed significantly between the two groups. However, this statistically significant beneficial reduction in fluorescein penetration into the left posterior vitreous did not occur in the right eye in the Cyclospasmol group. In placebo treated patients a consistently deleterious trend for this parameter was observed for both eyes during the one year study.(ABSTRACT TRUNCATED AT 250 WORDS)

MAIN MESH SUBJECTS:
Blood-Retinal Barrier/*DRUG EFFECTS
Cyclandelate/*THERAPEUTIC USE
Diabetic Retinopathy/*DRUG THERAPY
Mandelic Acids/*THERAPEUTIC USE

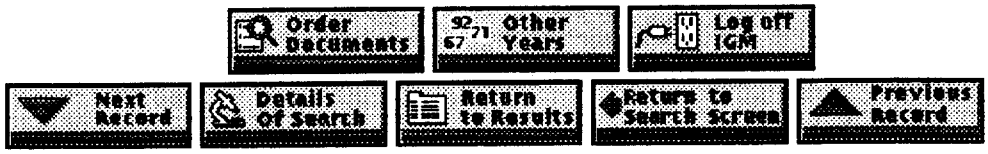
ADDITIONAL MESH SUBJECTS:	**Adolescence** **Adult** **Clinical Trials** **Double-Blind Method** **Female** **Human** **Male** **Middle Age** **Random Allocation** **Time Factors**
PUBLICATION TYPES:	**CLINICAL TRIAL** **JOURNAL ARTICLE** **RANDOMIZED CONTROLLED TRIAL**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Mandelic Acids)** **456-59-7 (Cyclandelate)**

ABSTRACT: Cyclandelate inhibits calcium-induced contraction of vascular smooth muscle cells, platelet aggregation induced by thrombin, platelet-activating-factor and adenosine, and also suppresses a provoked 5HT release from platelets. This pharmacological profile suggests that cyclandelate may have a potential prophylactic effect in migraine. To test this hypothesis, a double-blind multicentre study was performed in 214 patients to investigate the efficacy and tolerability of cyclandelate compared to placebo and propranolol. After a 4-week baseline period, eligible patients (randomization 3:2:3) were treated for 12 weeks with daily doses of 1.200 mg cyclandelate (n = 81), placebo (n = 55) or 120 mg propranolol (n = 78). The number of migraine attacks (> or = 50% responders) and the migraine duration/month were compared based on the difference between baseline and the last 4 weeks of prophylactic treatment. The percentage of patients with a reduction in migraine attacks of > or = 50% treated with cyclandelate (37.0%) or propranolol (42.3%) was not significantly superior to placebo (30.9%; p > 0.025). The mean duration of migraine in hours (h) per month decreased in both active treatment groups (cyclandelate: 36.8 h, p = 0.046; propranolol: 34.4 h, p = 0.039) compared to placebo (13.7 h) without reaching statistical significance (alpha/2 = 0.025). The clinical efficacy of cyclandelate and propranolol was comparable. Adverse experiences were reported by 13 patients (16.0%) treated with cyclandelate, by 5 patients (9.1%) treated with placebo and by 19 patients (24.4%) treated with propranolol. These were drug-related in 7.1% (n = 6) of patients treated with cyclandelate and in 9% (n = 7) of patients treated with propranolol. In summary, cyclandelate has a comparable efficacy to that of propranolol, an established drug of first choice in the prophylaxis of migraine. Both drugs were better than placebo, but not significantly so. Both active treatments were well tolerated.

MAIN MESH SUBJECTS:
Cyclandelate/*ADMINISTRATION & DOSAGE/ADVERSE EFFECTS
Migraine/*DRUG THERAPY
Propranolol/*ADMINISTRATION & DOSAGE/ADVERSE EFFECTS
Vasodilator Agents/*ADMINISTRATION & DOSAGE/ADVERSE EFFECTS

ADDITIONAL MESH SUBJECTS:
Adult
Comparative Study
Dose-Response Relationship, Drug
Double-Blind Method
Drug Administration Schedule
Female
Human
Male
Middle Age
Pain Measurement
Treatment Outcome

PUBLICATION TYPES:	**CLINICAL TRIAL** **JOURNAL ARTICLE** **MULTICENTER STUDY** **RANDOMIZED CONTROLLED TRIAL**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Vasodilator Agents)** **456-59-7 (Cyclandelate)** **525-66-6 (Propranolol)**



yclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol

HC Diener[1], M Föh[2], C Iaccarino[3], P Wessely[4], H Isler[5], H Strenge[6], M Fischer[7], W Wedekind[8], Z Taneri[9] on behalf of the study group*

Departments of Neurology, Universities of Essen[1]; Vienna[4]; Zürich[5]; Kiel[6]; Municipal Hospital, Fulda[2]; Neurological Practice, Naples[3]; Migraine Clinic, Duisburg[9]; Institute for Numerical Statistics, Cologne[7]; Medical Department of 3M Medica, Borken[8]

Cephalalgia

Diener HC, Föh M, Iaccarino C, Wessely P, Isler H, Strenge H, Fischer M, Wedekind W, Taneri Z. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. Cephalalgia 1996;16:441–7. Oslo. ISSN 0333–1024

Cyclandelate inhibits calcium-induced contraction of vascular smooth muscle cells, platelet aggregation induced by thrombin, platelet-activating-factor and adenosine, and also suppresses a provoked 5HT release from platelets. This pharmacological profile suggests that cyclandelate may have a potential prophylactic effect in migraine. To test this hypothesis, a double-blind multicentre study was performed in 214 patients to investigate the efficacy and tolerability of cyclandelate compared to placebo and propranolol. After a 4-week baseline period, eligible patients (randomization 3 : 2 : 3) were treated for 12 weeks with daily doses of 1.200 mg cyclandelate ($n=81$), placebo ($n=55$) or 120 mg propranolol ($n=78$). The number of migraine attacks (≥50% responders) and the migraine duration/month were compared based on the difference between baseline and the last 4 weeks of prophylactic treatment. The percentage of patients with a reduction in migraine attacks of ≥50% treated with cyclandelate (37.0%) or propranolol (42.3%) was not significantly superior to placebo (30.9%; $p>0.025$). The mean duration of migraine in hours (h) per month decreased in both active treatment groups (cyclandelate: 36.8 h, $p=0.046$; propranolol: 34.4 h, $p=0.039$) compared to placebo (13.7 h) without reaching statistical significance ($\alpha/2=0.025$). The clinical efficacy of cyclandelate and propranolol was comparable. Adverse experiences were reported by 13 patients (16.0%) treated with cyclandelate, by 5 patients (9.1%) treated with placebo and by 19 patients (24.4%) treated with propranolol. These were drug-related in 7.1% ($n=6$) of patients treated with cyclandelate and in 9% ($n=7$) of patients treated with propranolol. In summary, cyclandelate has a comparable efficacy to that of propranolol, an established drug of first choice in the prophylaxis of migraine. Both drugs were better than placebo, but not significantly so. Both active treatments were well tolerated. □ *Cyclandelate, double-blind, placebo, propranolol, prophylaxis of migraine, tolerability*

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Patients with frequent, prolonged and severe migraine attacks require migraine prophylaxis. A reduction in the frequency of attacks and the duration of migraine are two important aims. The mode of action of most drugs used in migraine prophylaxis is not known. Furthermore, no animal models are available to establish the mode of action of these medications. The prophylactic effect of beta-blockers, the most widely used drugs in the prophylaxis of migraine, was discovered by chance in patients treated for hypertension who at the same time suffered from migraine. Propranolol (1–6) has convincingly been shown to have migraine prophylactic activity. This activity has been confirmed by Holroyd et al. (7), who performed a meta-analysis of studies on propranolol in the prophylaxis of migraine. The 53 studies included 2403 patients who were treated with the beta-blocker propranolol (medium standard dose 160 mg/day) versus reference substances or placebo. On average, propranolol resulted in a 44% reduction in migraine activity when daily headache recordings were used to assess treatment outcome and in a 65% reduction of migraine activity when less conservative measures (e.g. clinical ratings of improvement, global patient reports) were used. The dropout rate due to side effects was 5.3%.

Cyclandelate inhibits provoked calcium overload in neurons (8), calcium-induced contraction of

Medical consultant: Haag, G., Windach. *Participating trial centres*: Beckmann-Reinholdt, A. ($n=29$)/Königstein; Langohr, H.H./Föh, M. ($n=26$)/Fulda; Iaccarino, C. ($n=24$)/Naples(I); Reinhardt, F. ($n=21$)/Pulsnitz; Taneri, Z./Thom, M. ($n=18$)/Duisburg; Wessely, P. ($n=16$)/Vienna(A); Meyer, Chr. ($n=11$)/Baden (CH); Haupt, G.E. ($n=9$)/Hofheim a.T.; Diener, H.C./May, A. ($n=8$)/Essen; Faust, W. ($n=8$)/Schopfheim; Isler, H./Lutz, J. ($n=8$)/Zürich(CH); Ribbat, M.J. ($n=8$)/Mainz; Scholz, E. ($n=7$)/Böblingen; Donat, P./[illegible], R. ($n=7$)/Duisburg; Kosanic, S./Schönbronn, E. ($n=7$)/[illegible]esheim; Gerber, W.D./Strenge, H. ($n=4$)/Kiel; Stosch, K. ($n=3$)/Aachen.

vascular smooth muscle cells (9–10), and platelet aggregation induced by thrombin, platelet activating factor (PAF) and adenosin (11). In addition, cyclandelate inhibits a provoked 5HT release from platelets (11–13) and protects against provoked cortical damage in a mouse model of focal ischaemia (14). This pharmacological profile suggests the likelihood of a prophylactic activity in migraine.

Earlier studies have indicated that cyclandelate given at a daily dosage of 1600 mg indeed has an anti-migraine prophylactic effect. In a small pilot trial (n=40), Nappi et al. (15) showed that cyclandelate was almost equally effective to flunarizine. Mastrosimone et al. (16) (n=84) described a significant superiority of cyclandelate to pizotifen. Gerber et al. (17) (n=84) observed a clinically relevant decrease in migraine symptoms with cyclandelate which was comparable to that of propranolol. Cyclandelate was well tolerated in all efficacy studies and exhibited the smallest incidence of adverse events compared to the reference drugs used (15–18).

Methods

To test the hypothesis that cyclandelate is more effective than placebo in the prophylaxis of migraine using the minimal effective dosage of 1200 mg/day, a randomized, parallel-group, double-blind multicentre study was performed. As a secondary hypothesis, comparative efficacy with propranolol (120 mg/day) was investigated. The study was approved by the respective local ethics committees.

Inclusion criteria

Patients between the age 18 and 60 years; male or female; migraine with and/or without aura according to the IHS criteria (19); migraine history of at least 12 months' duration; a mean number of 2–10 migraine attacks per month within the last 3 months prior to the study; and signed informed consent were admitted to the study.

Exclusion criteria

Pregnant or lactating women; psychiatric disorders; concomitant non-migraine headaches ≥3 times per month within the last 3 months; intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks preceding the trial; specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder); intake of drugs to treat migraine attacks>12 days/month. Prior to study entry and at the end of the treatment, the patients underwent physical and neurological examinations, including ECG and blood chemistry tests.

Design

Patients who fulfilled the entry criteria entered a 4-week baseline period without any prophylactic treatment. Those who recorded 2–10 attacks on their migraine headache diaries during the baseline period qualified for randomization (randomization ratio= 3 : 2 : 3) to cyclandelate, placebo or propranolol. To avoid early withdrawals due to initial side effects, treatment started with a 2-week run-in period at a dosage of 400 mg tid cyclandelate placebo or 40 mg tid propranolol. This was followed by a 12-week period of active prophylaxis at a dosage of 400 mg tid cyclandelate, placebo or 40 mg tid propranolol. The study ended with a 2-week run-out period to avoid early recurrence of migraine, using the same dosages as in the run-in period. Additional medication to treat acute migraine attacks was allowed for up to 12 days/month for the duration of the study, including the baseline period. Patients were required to come for a check-up visit at the end of the baseline period and at weeks 10, 14, 18 and 20 (Fig. 1).

Migraine headache diary

All patients kept a structured weekly diary and recorded daily migraine events: occurrence of migraine attacks; impairment of working ability; intensity of headache (measured by a visual analogue scale); duration of headache and migraine attack; intake of migraine medication during the attack; concomitant symptoms of migraine (e.g. photo- or phonophobia, nausea, autonomic disturbances, etc.). Patients were also asked to record adverse events related to the prophylactic medication. The attending physician was requested to transcribe the frequency and duration of migraine attacks and adverse events in the Case Report Forms (CRFs) at each visit.

Analysis of diaries

At the end of the study and prior to breaking the code, the attending physician evaluated all migraine headache diaries, blinded to the number and total duration of migraine attacks at baseline and in the last 4 weeks of prophylaxis. This diary database was used for primary analysis applying the following guidelines: (a) If migraine attacks occurred on two consecutive days within a time interval of less than 24 h, this was counted as one migraine attack; (b) the migraine duration was defined as the sum of all migraine hours documented by the patient in the diary within the 28 days preceding the end of baseline (week 4) and prophylactic treatment visits (week 18) (Fig. 1); (c) in cases where the patient was

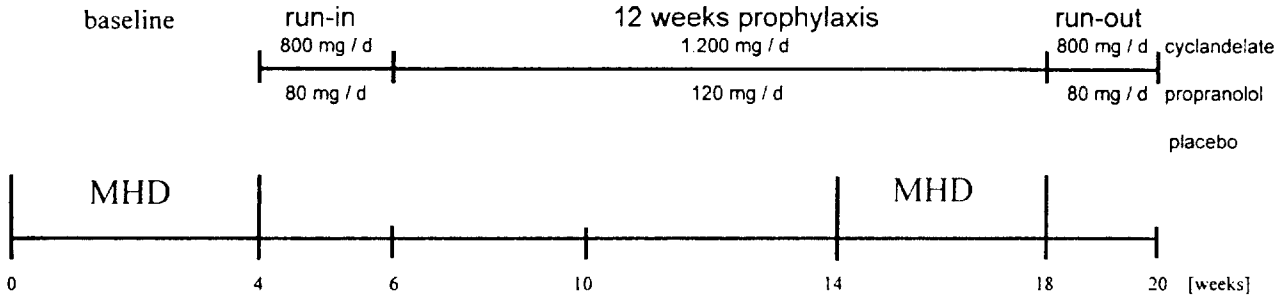

Fig. 1. Time course of the study, dosages and migraine evaluation.

run-in/run-out 2 weeks: cyclandelate 400 mg bid vs placebo vs propranolol 40 mg bid: 1-0-1 capsules/day
prophylaxis 12 weeks: cylandelate 400 mg tid vs placebo vs propranolol 40 mg tid: 1-1-1 capsules/day
MHD Migraine headache diary: evaluation 4 weeks baseline vs last 4 weeks of prophylaxis
1 ... 20 weeks scheduled check-up visits.

not able to distinguish between migraine and tension-type headaches, all additional concomitant symptoms documented in the diary were taken into consideration.

Endpoints and statistics

Two equivalent primary endpoints were defined: (a) "rate of responders", i.e. patients with ≥50% reduction in the number of migraine attacks; (b) mean migraine duration" in hours. The migraine parameters were calculated using the values of the last 4 weeks of the high-dosage period compared to those of the 4-week baseline period. Efficacy was assumed if cyclandelate showed significant superiority to placebo at an alpha-adjusted two-sided significance level of $\alpha/2=0.025$ in at least one of the two target criteria. Fisher's exact test and the *t*-test for independent samples were used as statistical methods for the rate of responders and migraine duration, respectively. Two patient populations were defined for statistical analysis, all randomized patients (intention-to-treat [ITT] group) and clinically relevant patients (per protocol [PP] group). All drop-outs after baseline were included in the intention-to-treat analysis on the basis of the last-value-carried-forward method.

Secondary endpoints were the efficacy of propranolol versus placebo and equivalent efficacy of cylandelate compared to propranolol. Additional secondary endpoints were change in intensity of headache, intake of analgesics or migraine drugs, number of working days lost due to migraine, frequency and severity of adverse events. For the secondary endpoints, adverse events and intake of acute migraine medication, only posthoc analyses are presented.

Case number of patients

Assuming a 60% response rate with cyclandelate and 30% with placebo and a reduction in migraine duration of 4 h with placebo and 8 h with cyclandelate with a standard deviation of 6 h, the sample size for cyclandelate and propranolol was calculated at $n=75$ and $n=50$ for placebo in the randomization ratio of 3 : 2 : 3. These case numbers are sufficient to find a statistically significant difference between cyclandelate (or propranolol) and placebo at $\alpha/2=0.025$ with a beta error of 20%.

Post-hoc analysis

The intake of medication to treat acute migraine attacks is known to be an accompanying critical issue for the evaluation of headache duration in clinical trials for prophylactic treatment. Therefore, all patients were stratified based on the intake of analgesics/antimigraine drugs during a defined number of weeks in the course of the trial. To obtain new insight into possibly different response properties of the ITT patient database, the ≥50% response criterion reduction of migraine duration was combined with the criterion "intake of acute medication over less than 5 weeks" during the 16 weeks of treatment (double response criterion).

Results

Study population

The study was initiated in November 1991 and finished in April 1994. Twenty-one screened patients did not qualify for randomization. A total of 214 ITT patients in 17 centres were randomized after completing the baseline period, 81 patients (37.9%) were treated with cyclandelate, 55 (25.7%) with placebo and 78 (36.4%) with propranolol. Forty patients had to be excluded from the ITT analysis for various reasons (Table 1) and 174 patients (cyclandelate $n=67$, placebo $n=39$, propranolol $n=68$) remained for the PP analysis.

Table 1. Patients violating protocol requirements.

Reasons for exclusion from ITT database	$n=40$
Early study termination/not drug-related	$n=15$
≤2 attacks during baseline period (one <24 h)	$n=8$
Evaluation of diary not possible	$n=7$
Control visit missed by >2 weeks	$n=6$
Intake of additional medication ≥15 days/4 weeks	$n=2$
Age <18 or >60 years	$n=2$

Demographic and baseline data (Table 2)

The three treatment groups were comparable in terms of age, distribution of gender and history of migraine (Table 2). The three treatment groups were comparable with regard to number of attacks/4 weeks, intensity of pain during attacks and intake of acute migraine medication. The mean duration of migraine in hours/4 weeks and the standard deviation was slightly greater in the cyclandelate group than in the placebo and propranolol groups. However, the differences did not reach statistical significance.

Withdrawals after randomization

Thirty-six patients (16.8%) dropped out after randomization (cyclandelate $n=16$, placebo $n=8$, propranolol $n=12$). The frequency of withdrawals under cyclandelate and propranolol was comparable, but numerically higher compared to placebo in the efficacy-related and possibly drug-related reasons. The overall distribution of all reasons for withdrawals is given in Table 3.

Efficacy

Primary endpoints

The first primary endpoint (≥50% reduction of migraine attacks) was met by 30/81 (37.0%) patients treated with cyclandelate and 17/55 (30.9%) patients treated with placebo. There was no significant difference between the two groups ($p>0.025$). In the propranolol group the response criterion was fulfilled by 33/78 (42.3%, $p>0.05$ vs placebo) patients. Similar results were obtained for the per protocol analysis (Fig. 2).

The mean absolute reduction of migraine duration/4 weeks (second primary endpoint) was 36.8±73.7 h with cyclandelate compared to

Table 2. Comparison of the three treatment groups.

Patient characteristics	Total $n=214$	Cyclandelate $n=81$	Propranolol $n=78$	Placebo $n=55$
Demographic and baseline data				
Mean age (years)	39±12	39±12	40±13	39±11
Sex				
Women	167/78.0%	66/81.5%	60/76.9%	41/74.5%
Men	47/22.0%	15/18.5%	18/23.1%	14/25.5%
Mean migraine history since (years)	19±12	18±12	21±13	19±11
Migraine with aura	56/26.2%	24/29.6%	18/23.1%	14/25.5%
Migraine without aura	156/72.9%	56/69.1%	59/75.6%	41/74.5%
Migraine with + without aura	2	1	1	0
No. of patients with acute migraine medication:				
Analgesics/antirheumatics	142/66.4%	55/67.9%	51/65.4%	36/65.5%
Specific migraine drugs	127/59.3%	46/56.8%	49/62.8%	32/58.2%
		Cyclandelate	Propranolol	Placebo
Migraine baseline data				
Mean number of attacks/4 weeks		4±1	4±2	4±2
≤4 attacks		3±1	3±1	3±1
Mean migraine duration/4 weeks (h)		88±79	81±50	73±41
≤4 attacks		81±79	69±46	71±42
Pain intensity during attack				
Severe		27/33.3%	26/33.3%	17/30.9%
Moderate		51/63.0%	49/62.8%	31/56.4%
Mild		3/3.7%	3/3.8%	7/12.7%
Additional medication during attacks				
Never		6/7.4%	3/3.8%	2/3.6%
Sometimes		23/28.4%	24/30.8%	15/27.3%
Every attack		52/64.2%	51/65.4%	38/69.1%

le 3. Reasons for withdrawal

Reason No. of patients (%)	Total $n=214$ $n=36$ (16.8%)	Cyclandelate $n=81$ $n=16$ (19.8%)	Propranolol $n=78$ $n=12$ (15.4%)	Placebo $n=55$ $n=8$ (14.4%)
Not drug-related	15 (7.0%)	5 (6.2%)	3 (3.8%)	7 (12.7%)
Efficacy-related (total)	8 (3.7%)	5 (6.2%)	3 (3.8%)	–
Complete relief	2 (0.9%)	2 (2.5%)	–	–
Lack of efficacy	6 (2.8%)	3 (3.7%)	3 (3.8%)	–
Adverse events (no. of patients)	13 (6.1%)	6 (7.4%)	6 (7.7%)	1 (1.8%)
Side effects	9 (4.2%)	5 (6.2%)	4 (5.1%)	–

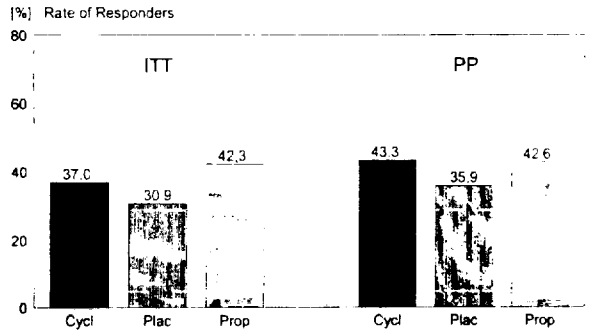

Fig. 2. Rate of responders (≥50% reduction of attack frequency/4 weeks) compared to baseline.

ITT=Intention-to treat PP=per Protocol
Cycl=cylandelate Plac=placebo Prop=propranolol
*$p>0.05$; $\alpha/2=0.025$ (Fisher's exact test, 2-sided).

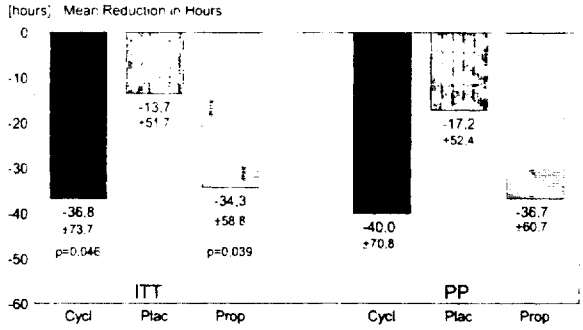

Fig. 3. Mean absolute reduction of migraine duration/4 weeks compared to baseline.

ITT=Intention-to treat PP=per Protocol
Cycl=cyclandelate Plac=Placebo Prop=Propranolol
*$p>0.05$; $\alpha/2=0.025$ (t-test for independent samples, 2-sided.

13.7±51.7 h with placebo ($p=0.046$). Propranolol reduced the migraine duration on average by 34.6±58.8 h ($p=0.039$). These results were clinically relevant for both active drugs, but failed to achieve the adjusted significance level of $\alpha/2=0.025$ (ITT). Similar results were obtained for the per protocol analysis (Fig. 3).

Secondary endpoints

Equivalence of cyclandelate and propranolol. No significant statistical equivalence of cyclandelate and propranolol was found in either main efficacy criteria ($p=0.05$, 1-sided).

Post hoc analysis

The analysis of the subgroup of patients that fulfilled the response criterion of a ≥50% reduction of migraine duration with an intake of acute medication over less than 5 weeks during the course of the study showed cyclandelate to be significantly superior to placebo (32.1% vs 12.7%, $p=0.014$) in contrast to propranolol (19.2%, $p>0.05$). The analysis of the complementary responder groups with an intake of acute medication during more than 5 weeks did not show any significant difference between placebo and active drug.

The 1-sided equivalence test showed significant equivalence of cyclandelate and propranolol in the reduction of migraine duration (32.1% vs 19.2%, $p=0.007$).

Tolerability/side effects

Blood pressure and blood chemistry remained unchanged throughout the trial in all three treatment groups. In the propranolol group the heart rate was reduced on average by 5 beats/min. Thirteen of 81 (16.0%) patients treated with cyclandelate, 5 of 55 (9.1%) patients with placebo and 19 of 78 (24.4%) patients with propranolol reported adverse events. Of these adverse events, a total of 16 events in 13 patients were probably drug-related side effects (Table 4). Five patients in the cyclandelate group and 4 patients in the propranolol group withdrew from the study due to side effects.

Table 4. Side effects.

Total no.	Cyclandelate 81	Propranolol 78
No. of side effects	9	7
No. of patients with side effects	6	7
Type of side effects	Increased sweating Hypertension Sleep difficulty Depressed mood Drowsiness Gastric pain (2) Respiratory difficulty Kidney pain	Depressed mood Gastric pain (2) Gastric spasm Gastric difficulty Diarrhea Bradycardia

Discussion

The goal of this study was to investigate the efficacy of cyclandelate compared with placebo and propranolol on the basis of intention-to-treat and per protocol analyses. The prophylactic treatment showed no statistical superiority of either cyclandelate or propranolol over placebo in the reduction of frequency of attacks. The duration of migraine per month was reduced by both active drugs to a clinically but not statistically significant degree. Overall, the clinical reduction of migraine parameters for both prophylactic drugs was comparable, confirming the previous report of Gerber et al. (17).

The placebo effect in this study was somewhat high (31% for frequency and 19% for duration) but comparable to previously reported figures, i.e. 20–40% for change in headache frequency (20) and 12±15% for headache duration (7).

We have attempted to overcome the ambiguous and variable recordings in some patients' diaries by using a standardized procedure (see Methods section) aimed at including the largest possible number of evaluable data points in the final analysis. The same evaluation procedure was applied in all three treatment arms before breaking the code. Thus it is unlikely that such a technique would bias the results in favour of one treatment but not the other(s).

We considered that methodological errors could have accounted for the outcome of the study. Accordingly, we performed two post-hoc analyses. In the first, the double response criterion showed a significant superiority of cyclandelate over placebo in migraine duration, which is more pronounced than for propranolol. This stable result suggests that the assessment of efficacy of migraine prophylactic drugs should include a responder population encompassing both the reduction of migraine duration and additional medication responders with a reduced intake of drugs to treat acute migraine attacks. Further studies need to be conducted to confirm this hypothesis. In the second post hoc analysis, the patients who took sumatriptan ($n=34$) were excluded from the ITT database. Subsequently, we found that cyclandelate and propranolol were better than placebo ($p=0.024$ and 0.026, respectively) in reducing the mean duration of migraine attacks.

The incidence of adverse events was lower with cyclandelate than with propranolol, but drug-related side effects were comparable. These results confirm the good tolerability of cyclandelate reported in earlier studies (15–18). Furthermore, and in contrast with most other substances for migraine prophylaxis, cyclandelate has no specific contraindications other than acute stroke and glaucoma. It could be used in patients with contraindications for other prophylactic drugs (e.g. overweight, asthmatic patients, and patients with coronary heart disease).

Our study demonstrates that cyclandelate and propranolol are equally effective medications in migraine prophylaxis, but not better than placebo. Cyclandelate is well tolerated.

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Treatment of early diabetic retinopathy with cyclandelate

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SUMMARY In order to assess the effect of cyclandelate on the abnormal permeability of the blood-retinal barrier which occurs in diabetic patients before any other lesions are apparent in the retina a well-controlled, double blind, and paired trial was carried out in 22 patients. The treatments were randomised. The permeability of the blood-retinal barrier was assessed by vitreous fluorophotometry. Each patient was examined before being involved in the trial and then another 3 times with 1 month's interval. The total duration of treatment was 3 months.

The results showed that the breakdown of the blood-retinal barrier as evidenced by the degree of abnormal fluorescein penetration into the vitreous suffered a significant decrease in the diabetic patients treated with cyclandelate when compared to the patients submitted to placebo administration and this effect is particularly apparent in the third month of treatment.

It is now widely recognised that the major problem in diabetes mellitus does not arise acutely from lack of control of the carbohydrate metabolism, but from the insidiously developing vascular complications (Ditzel and Standl, 1975). The morbidity and incapacity associated with these complications are staggering, this being particularly true with diabetic retinopathy, which is nowadays one of the major causes of blindness.

In order to prevent this dramatic outcome it is necessary to detect the disease at a very early stage and to develop means of stopping its further progress. Its detection at a reversible stage and its immediate and effective treatment would be ideal.

It has recently been shown by our group that a significant disturbance of the blood-retinal barrier is present in diabetic patients with apparently normal fundi, this disturbance being apparently reversible (Cunha-Vaz *et al.*, 1975). This was made possible by the introduction of vitreous fluorophotometry, a new clinical quantitative method for the study of the blood-retinal barrier.

There is also some evidence that from the early onset of the disease diabetics may suffer from inumerable cellular hypoxic injuries, caused by the association of an increase in oxygen demand (Joslin, 1923; White, 1939) and a disordered oxygen delivery (Ditzel and Rooth, 1955; Ditzel and Standl, 1975b).

It is therefore reasonable to consider the possibility that the oxygen-dependent active transport mechanisms of the blood-retinal barrier are altered by these fluctuations in tissue oxygen tension and that any drug which has a protective action against hypoxia may influence favourably the course of the disease.

Cyclandelate was the drug chosen for this trial because it has been shown to have a protective action against brain hypoxia (Funcke *et al.*, 1974). In the past 10 years a number of papers have been published in which it was shown that cyclandelate treatment was followed by dilatation of cerebral vessels (Kuhn, 1966) and increased cerebral circulation (O'Brien and Veall, 1966). Improvement of mental functions in geriatric patients treated with the drug has been noted by Drift (1961), Ball and Taylor (1967), and others. These studies pointed, however, to an effect or effects of the drug on cerebral metabolism other than those indicated by a direct action on the tone of cerebral blood vessels. It has, indeed, been shown recently that cyclandelate enhances the resistance of rats and mice to hypoxia and attenuates or prevents the disturbances in the EEG of rats due to lack of oxygen (Funcke *et al.*, 1974). Cyclandelate has also been shown to increase the penetration of glucose

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into rat brain, and it is now accepted that the therapeutic efficacy of cyclandelate in cerebrovascular insufficiency may be based not merely on improved blood flow but also on stimulation of active glucose uptake by the brain.

The aim of this study is therefore to assess the effect of cyclandelate on the permeability of the blood-retinal barrier in diabetic patients, before there are any apparent retinal lesions, and when a complete recovery may be expected.

Method and evaluation

The trial was started as well-controlled, double blind, and paired and completed as such. The treatments were randomised. The parameter measured was the permeability of the blood-retinal barrier as evidenced by the penetration of fluorescein after intravenous injection.

The trial was carried out with adult diabetic patients which were being followed up as outpatients in the Diabetes Clinic of Coimbra University Hospital. There were 6 men and 16 women, ranging from 26 to 80 years of age, and averaging 52·4 years. Patients having a history of eye disease or showing any retinal lesions were excluded from this trial. Only patients with maximal visual acuity, normal ophthalmoscopic and slit-lamp pictures, and normal retinal fluorescein angiography were admitted to the population.

Patients were admitted to the trial in 12 pairs. One member of each pair was treated with cyclandelate and the other with placebo. A patient who dropped out during the course of the trial was replaced, as well as the other from that pair. One of these pairs dropped out, however, only in the last month of the trial and could not be replaced. By the end of the trial there were, therefore, 11 pairs.

The details of the trial were explained to each patient and consent was obtained. Each individual was assigned to either cyclandelate or placebo, as determined by a table of random numbers.

The doses of cyclandelate were standardised at 400 mg/capsule, 4 times daily. The total treatment duration was 3 months. The capsules of cyclandelate and placebo were provided by Mycopharma-Brocades. The key to the randomisation codes was kept by the local pharmacist and was unknown to the examiners until the trial was completed. No other preparation with vascular effects was used by the patients during the course of the trial.

Assessment of the permeability of the blood-retinal barrier

The permeability of the blood-retinal barrier was assessed by vitreous fluorophotometry (Cunha-Vaz *et al.*, 1975). The apparatus consisted essentially in a model 360 Haag-Streit slit-lamp which was modified by adapting a new source of illumination, appropriate filters, a photometric detection system, and a device for electrical registration of the movement of the instrument. Each patient was assessed 4 times the first, before being involved in the trial, the second, at the end of the first month, the third at the end of the second month, and the fourth after the 3-month treatment. For these examinations a 10 ml intravenous injection of 10% sodium fluorescein was immediately followed by fluorescence angiography, performed with the Topcon TRC-F3 and by vitreous fluorophotometry 1 hour later. The fluorophotometric curves were recorded by a Polaroid camera. Because the values in the anterior vitreous, near the lens, are variable and influenced by fluorescein penetration through anterior routes, only the posterior half of the curve was analysed. The lower area A as indicated in Fig. 1 was roughly integrated, this value representing a true value of the concentration of fluorescein in the posterior vitreous.

The values obtained for these areas in each patient are presented in Table 1. These areas were named A_0, A_1, A_2, and A_3, according to the occasion of their recording, before the trial, after the first month, after the second month, or at the end of the third month, respectively.

The mean values of areas 0, 1, 2, and 3 in each group of patients were first compared in order to detect any general difference in behaviour between the 2 groups.

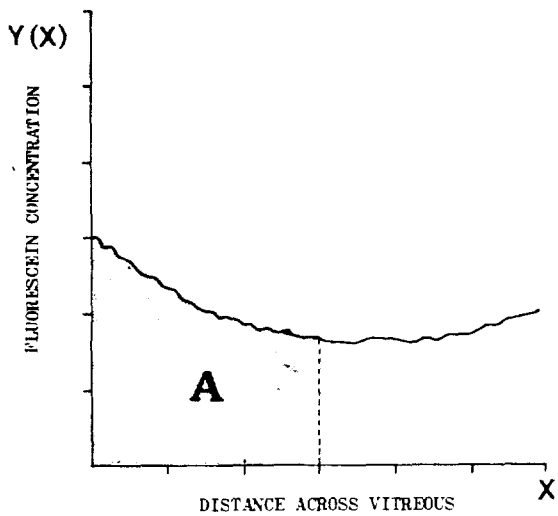

Fig. 1 *Typical fluorophotometric curve. The lower area, A under the curve represents a true value of the concentration of fluorescein in the posterior vitreous*

Table 1 *Values of fluorescein penetration into the posterior vitreous in the 4 examinations during the 3-month trial*

Placebo							*Cyclandelate*						
S. No.	*Age/Sex*	*Fluorescein penetration*				*Clinical information*	*S. No.*	*Age/Sex*	*Fluorescein penetration*				*Clinical information*
		A_0	A_1	A_2	A_3				A_0	A_1	A_2	A_3	
1	60/F	6·1	7·3	9·2	9·2		2	59/F	3·7	6·7	8·3	7·5	
4	50/F	5·4	4·1	6·9	7·0		3	80/F	9·3	9·4	11·9	10·2	
6	47/M	4·4	4·0	6·6	5·9		5	51/F	4·8	5·9	9·4	9·7	
8	42/F	3·3	6·7	5·7	8·4		7	55/M	4·6	6·3	9·1	9·1	Minimal hard exudates
9	33/F	6·7	6·5	6·6	6·9		10	26/F	5·4	7·9	4·7	4·8	
12	68/M	7·5	7·6	8·4	9·6		11	57/M	6·2	6·0	7·1	4·9	
15	64/F	5·9	5·9	9·2	10·3	Minimal hard exudates	16	42/F	7·8	6·0	7·0	5·4	
18	44/M	4·4	4·0	5·5	5·5		17	66/F	4·7	7·0	8·2	8·2	
20	46/F	3·6	6·8	10·2	9·1		19	60/F	4·6	6·1	7·6	6·5	
21	49/M	1·7	3·7	5·3	7·6	Hard exudates; signs of leakage on angiography	22	50/F	2·2	3·6	7·5	4·9	
26	42/F	4·8	4·0	8·7	10·0	Signs of leakage on angiography	25	61/F	6·0	6·4	7·7	6·7	
Mean		4·89	5·51	7·48	8·14				5·39	6·48	8·05	7·08	

The parameter that was used to test efficacy of the drug *v.* the placebo was the difference between the fluorescein concentrations in the posterior ...ous at the final examination, represented by A_3, the fluorescein concentrations at the previous visits (A_2, A_1, and A_0).

For each patient (11 drug, 11 placebo) these differences ($A_3 - A_0$, $A_3 - A_1$, and $A_3 - A_2$) were subjected to statistical analysis. A final complementary analysis was made taking into account simultaneously for each patient, the differences $A_1 - A_0$ and $A_3 - A_2$, in order to highlight the corrective action of the drug on the abnormal permeability of the blood-retinal barrier. $A_1 - A_0$ represents the natural evolution of the disease, the effect of treatment being then minimal; $A_3 - A_2$ represents best the effect of treatment.

The following standard statistical methods were used: Student's *t* test and standard deviation.

CLINICAL ASSESSMENT

The visual acuity was tested for each patient and he was examined 4 times by ophthalmoscopy, during the course of the trial, at the beginning and at the end of each month.

Results

Assessment of the permeability of the blood-retinal barrier by vitreous fluorophotometry

The mean values of the areas under the fluorophotometric curves, representing the fluorescein penetration into the posterior half of the vitreous, ...tained from each patient (11 placebo, 11 cyclan...te) and from the 4 examinations were graphically plotted (Fig. 2). The figure shows a well-defined pattern of progressive increase in the permeability of the blood-retinal barrier, well evidenced by the increased fluorescein penetration into the vitreous, in the placebo-treated patients, during the 3-month period of the trial. This pattern appeared, however, to be completely inverted during the third month of treatment in the patients receiving cyclandelate, suggesting a definite improvement in the conditions of abnormal permeability of the blood-retinal barrier which characterises the early stages of retinal involvement in diabetes.

Fig. 2 *Patterns of fluorescein penetration into the posterior vitreous, in placebo and cyclandelate treated patients, during the 3-month trial*

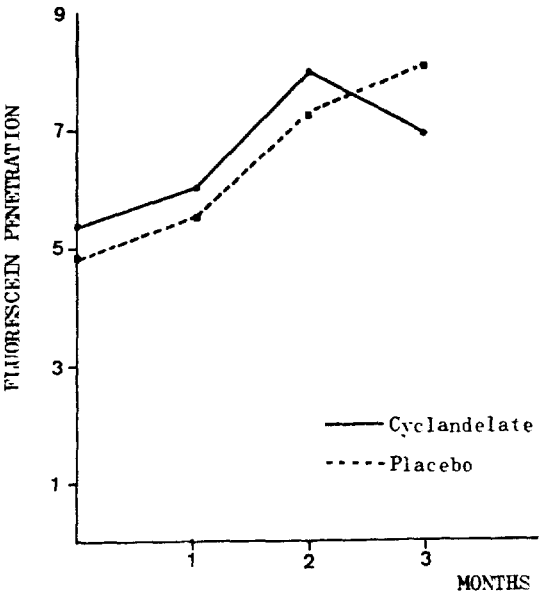

Table 2 *Differences in fluorescein penetration into the posterior vitreous between the last (A_3) and the initial examination (A_0)*

Placebo		*Cyclandelate*	
Series No.	$A_3 - A_0$	*Series No.*	$A_3 - A_0$
1	+3·1	2	−3·8
4	−1·6	3	−0·9
6	−1·5	5	−4·9
8	−5·1	7	−4·5
9	−0·2	10	−0·6
12	−2·1	11	−1·3
15	−4·4	16	−2·4
18	−1·1	17	−3·5
20	−5·5	19	−1·9
21	−5·9	22	−2·7
26	−5·2	25	−0·7
Mean	−3·2		−1·6
±SD	±0·616		±0·736

$t = 1{\cdot}74$; DF = 20; $0{\cdot}1 < P > 0{\cdot}05$.

Table 4 *Differences in fluorescein penetration into the posterior vitreous between the end of the trial (A_3) and the end of the second month (A_2)*

Placebo		*Cyclandelate*	
Series No.	$A_3 - A_2$	*Series No.*	$A_3 - A_2$
1	0	2	−0·8
4	+0·1	3	−1·7
6	−0·7	5	−0·3
8	−2·7	7	0
9	−0·3	10	−0·1
12	+1·2	11	−2·2
15	−1·1	16	−1·6
18	0	17	0
20	−1·1	19	−1·1
21	−2·3	22	−2·6
26	−1·3	25	−1·0
Mean	−0·65		−0·96
±SD	±0·357		±0·298

$t = 3{\cdot}6$; DF = 20; $0{\cdot}005 < P > 0{\cdot}001$.

This finding is substantiated when the differences in fluorescein concentration in the posterior vitreous between the last and the previous visits were analysed and the values obtained from patients given placebo capsules compared with the values obtained from cyclandelate-treated patients. The differences in fluorescein penetration, i.e., breakdown of the blood-retinal barrier, between the last visit (A_3) and the initial examination (A_0) are significantly different at the 10% level between the 2 groups of patients, placebo and cyclandelate ($t = 1{\cdot}74$; DF = 20; $0{\cdot}1 < P > 0{\cdot}05$; Table 2).

This level of significance increases, however, when the differences in fluorescein penetration are taken between the last visit and the second and third examinations, after 1 and 2 months of treatment, respectively. The differences between the last visit and the second examination ($A_3 - A_1$), between the 2 groups of patients, are significant at the 2% level ($t = 2{\cdot}7$; DF = 20; $0{\cdot}02 < P > 0{\cdot}01$; Table 3). Finally,

Table 3 *Differences in fluorescein penetration into the posterior vitreous between the end of the trial (A_3) and the end of the first month (A_1)*

Placebo		*Cyclandelate*	
Series No.	$A_3 - A_1$	*Series No.*	$A_3 - A_1$
1	−1·9	2	+0·8
4	−2·9	3	+0·8
6	−1·9	5	−3·8
8	−1·7	7	−2·8
9	−0·4	10	−3·1
12	−2·0	11	−1·1
15	−4·4	16	−0·6
18	−1·5	17	−1·2
20	−2·3	19	−0·4
21	−3·9	22	+1·3
26	−6·0	25	+0·3
Mean	−2·6		−0·6
±SD	±0·475		±0·534

$t = 2{\cdot}7$; DF = 20; $0{\cdot}02 < P > 0{\cdot}01$.

the differences between the final observation and the third examination ($A_3 - A_2$) show a highly significant difference between the 2 groups of patients ($t = 3{\cdot}6$; DF = 20; $0{\cdot}005 < P > 0{\cdot}001$; Table 4). These results show clearly that cyclandelate has a beneficial effect upon the breakdown of the blood-retinal barrier which is present in the early stages of diabetic retinopathy, preventing its progressive increase, well evidenced in patients receiving placebo capsules. The results indicate also that this beneficial effect is particularly marked after a period of treatment of 2 months. The fact that the full effect of cyclandelate is especially well evidenced in the third month of treatment, in contrast to the first month when its activity appears to be minimal, prompted us to compare the differences between the third month of treatment ($A_3 - A_2$) and the first month ($A_1 - A_0$), i.e. $(A_3 - A_2) - (A_1 - A_0)$ between the 2 groups. The statistical analysis of these differences shows a highly significant difference between the 2 groups ($t = 4{\cdot}4$; DF = 20; $P < 0{\cdot}001$; Table 5).

These results indicate clearly that the breakdown of the blood-retinal barrier as evidenced by the degree of abnormal fluorescein penetration into the vitreous suffered a significant decrease in the diabetic patients treated with cyclandelate when compared to the patients submitted to placebo administration, and that this effect is particularly apparent after 2 months of treatment.

CLINICAL ASSESSMENT

The other examinations performed agree, although in a less clear manner, with the fluorophotometric results. As regards the clinical picture, the cases under study are of such nature that only signs of worsening can be accepted as true changes. The visual acuity remained maximal in every patient

Table 5 *Differences in fluorescein penetration between the third month of the trial ($A_3 - A_2$) and the first month ($A_1 - A_0$)*

Placebo				*Cyclandelate*			
Series No.	$A_3 - A_2$	$A_1 - A_0$	*Difference*	*Series No.*	$A_3 - A_2$	$A_1 - A_0$	*Difference*
1	0	−1·2	−1·2	2	−0·8	−3·0	−3·8
4	−0·1	−1·3	−1·2	3	−1·7	−0·1	−1·8
6	−0·7	−0·4	−0·3	5	−0·3	−1·1	−0·8
8	−2·7	−3·4	−0·7	7	0	−1·7	−1·7
9	−0·3	−0·2	−0·5	10	−0·1	−2·5	−2·6
12	−0·6	−0·1	−0·5	11	−2·2	−0·2	−2·0
15	−1·1	0	−1·1	16	−1·6	−1·8	−0·2
18	0	−0·4	−0·4	17	0	−2·3	−2·3
20	−1·1	−3·2	−2·1	19	−1·1	−1·5	−2·6
21	−2·3	−2·0	−0·3	22	−2·6	−1·4	−4·0
26	−1·3	−0·8	−0·5	25	−1·0	−0·4	−1·4
Mean			−0·02				−2·07
SD			±0·302				±0·455

$t = 4·4$; DF = 20; $P < 0·001$.

during the entire trial. Ophthalmoscopically and angiographically, however, slight changes developed in the fundi of 3 patients receiving placebo and in 1 patient receiving cyclandelate (Table 1). These included the development of minimal hard exudates and some angiographical evidence of fluorescein leakage. The angiographical changes were observed in 2 placebo patients at the last examination, whereas the hard exudates were seen with the ophthalmoscope in 3 placebo-treated patients and in only 1 receiving cyclandelate. An overall clinical impression was, therefore, obtained of more marked progression of the retinal involvement in the diabetics not receiving cyclandelate.

SIDE-EFFECTS

Two patients complained of nausea. This was sufficient to provoke in 1 patient discontinuation of treatment and the consequent dropping out of the respective pair and its substitution with a new pair. It is interesting, however, to note that the second patient who complained of nausea was receiving the placebo capsules.

Discussion

The present trial has shown that cyclandelate in doses of 400 mg capsule, 4 times daily, given for a period of 3 months, has significant beneficial effect upon the breakdown of the blood-retinal barrier which is present in the early stages of retinal involvement in diabetes. The use of vitreous fluorophotometry, a clinical quantitative method of evaluation of the permeability of the blood-retinal barrier, allowed the results to be subjected to statistical analysis. This showed that the progressive deterioration of the blood-retinal barrier observed in the diabetic patients receiving placebo capsules during the 3-month trial was arrested in the patients receiving cyclandelate. This beneficial effect of cyclandelate was particularly marked in the third month of treatment, when the levels of breakdown of the blood-retinal barrier decreased significantly, pointing to some recovery of the disease process, and suggesting even better results from prolonged periods of treatment. In a less clear manner the clinical impression obtained from ophthalmoscopy and fluorescence angiography agreed with the results obtained, showing an apparently more rapid progression of the disease in the placebo-treated diabetics. It remains now to be seen if these results can be confirmed by long-term studies and if the progression and development of the full picture of diabetic retinopathy and final loss of vision can be prevented by prolonged treatment with cyclandelate.

The results here reported showing a favourable effect of cyclandelate on the abnormal permeability of the blood-retinal barrier in the earlier stages of diabetic retinopathy are probably due to the protective action of the drug against hypoxia (Funcke *et al.*, 1974). It is to be recalled that an increase in retinal blood flow by direct action on the tone of the retinal vessels would not appear to have any beneficial effect, according to recent personal observations (Cunha-Vaz *et al.*, 1977), which showed an apparent direct correlation between increase in retinal blood flow and progression of diabetic retinopathy.

The demonstration of a beneficial effect of cyclandelate in early diabetic retinal involvement supports the work of Ditzel and Standl (1975a, b) and substantiates the hypothesis that fluctuations in tissue oxygen tension may be responsible for the retinal vascular complications in diabetes. Examination of the effect of this drug upon other vascular complications of diabetes may help to indicate if

these variations in tissue oxygen tension are a general phenomenon of paramount importance in every vascular complication of diabetes or if they assume a particular significance in the retina, a tissue well known for its high metabolic needs.

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Treatment of early diabetic retinopathy with cyclandelate

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SUMMARY In order to assess the effect of cyclandelate on the abnormal permeability of the blood-retinal barrier which occurs in diabetic patients before any other lesions are apparent in the retina a well-controlled, double blind, and paired trial was carried out in 22 patients. The treatments were randomised. The permeability of the blood-retinal barrier was assessed by vitreous fluorophotometry. Each patient was examined before being involved in the trial and then another 3 times with 1 month's interval. The total duration of treatment was 3 months.

The results showed that the breakdown of the blood-retinal barrier as evidenced by the degree of abnormal fluorescein penetration into the vitreous suffered a significant decrease in the diabetic patients treated with cyclandelate when compared to the patients submitted to placebo administration and this effect is particularly apparent in the third month of treatment.

It is now widely recognised that the major problem in diabetes mellitus does not arise acutely from lack of control of the carbohydrate metabolism, but from the insidiously developing vascular complications (Ditzel and Standl, 1975). The morbidity and incapacity associated with these complications are staggering, this being particularly true with diabetic retinopathy, which is nowadays one of the major causes of blindness.

In order to prevent this dramatic outcome it is necessary to detect the disease at a very early stage and to develop means of stopping its further progress. Its detection at a reversible stage and its immediate and effective treatment would be ideal.

It has recently been shown by our group that a significant disturbance of the blood-retinal barrier is present in diabetic patients with apparently normal fundi, this disturbance being apparently reversible (Cunha-Vaz *et al.*, 1975). This was made possible by the introduction of vitreous fluorophotometry, a new clinical quantitative method for the study of the blood-retinal barrier.

There is also some evidence that from the early onset of the disease diabetics may suffer from inumerable cellular hypoxic injuries, caused by the association of an increase in oxygen demand (Joslin, 1923; White, 1939) and a disordered oxygen delivery (Ditzel and Rooth, 1955; Ditzel and Standl, 1975b).

It is therefore reasonable to consider the possibility that the oxygen-dependent active transport mechanisms of the blood-retinal barrier are altered by these fluctuations in tissue oxygen tension and that any drug which has a protective action against hypoxia may influence favourably the course of the disease.

Cyclandelate was the drug chosen for this trial because it has been shown to have a protective action against brain hypoxia (Funcke *et al.*, 1974). In the past 10 years a number of papers have been published in which it was shown that cyclandelate treatment was followed by dilatation of cerebral vessels (Kuhn, 1966) and increased cerebral circulation (O'Brien and Veall, 1966). Improvement of mental functions in geriatric patients treated with the drug has been noted by Drift (1961), Ball and Taylor (1967), and others. These studies pointed, however, to an effect or effects of the drug on cerebral metabolism other than those indicated by a direct action on the tone of cerebral blood vessels. It has, indeed, been shown recently that cyclandelate enhances the resistance of rats and mice to hypoxia and attenuates or prevents the disturbances in the EEG of rats due to lack of oxygen (Funcke *et al.*, 1974). Cyclandelate has also been shown to increase the penetration of glucose

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into rat brain, and it is now accepted that the therapeutic efficacy of cyclandelate in cerebrovascular insufficiency may be based not merely on improved blood flow but also on stimulation of active glucose uptake by the brain.

The aim of this study is therefore to assess the effect of cyclandelate on the permeability of the blood-retinal barrier in diabetic patients, before there are any apparent retinal lesions, and when a complete recovery may be expected.

Method and evaluation

The trial was started as well-controlled, double blind, and paired and completed as such. The treatments were randomised. The parameter measured was the permeability of the blood-retinal barrier as evidenced by the penetration of fluorescein after intravenous injection.

The trial was carried out with adult diabetic patients which were being followed up as outpatients in the Diabetes Clinic of Coimbra University Hospital. There were 6 men and 16 women, ranging from 26 to 80 years of age, and averaging 52·4 years. Patients having a history of eye disease or showing any retinal lesions were excluded from this trial. Only patients with maximal visual acuity, normal ophthalmoscopic and slit-lamp pictures, and normal retinal fluorescein angiography were admitted to the population.

Patients were admitted to the trial in 12 pairs. One member of each pair was treated with cyclandelate and the other with placebo. A patient who dropped out during the course of the trial was replaced, as well as the other from that pair. One of these pairs dropped out, however, only in the last month of the trial and could not be replaced. By the end of the trial there were, therefore, 11 pairs.

The details of the trial were explained to each patient and consent was obtained. Each individual was assigned to either cyclandelate or placebo, as determined by a table of random numbers.

The doses of cyclandelate were standardised at 400 mg capsule, 4 times daily. The total treatment duration was 3 months. The capsules of cyclandelate and placebo were provided by Mycopharma-Brocades. The key to the randomisation codes was kept by the local pharmacist and was unknown to the examiners until the trial was completed. No other preparation with vascular effects was used by the patients during the course of the trial.

Assessment of the permeability of the blood-retinal barrier

The permeability of the blood-retinal barrier was assessed by vitreous fluorophotometry (Cunha-Vaz *et al.*, 1975). The apparatus consisted essentially in model 360 Haag-Streit slit-lamp which was modifie by adapting a new source of illumination, appropr ate filters, a photometric detection system, and device for electrical registration of the movement the instrument. Each patient was assessed 4 time the first, before being involved in the trial, th second, at the end of the first month, the third at th end of the second month, and the fourth after th 3-month treatment. For these examinations 10 ml intravenous injection of 10% sodium fluore scein was immediately followed by fluorescenc angiography, performed with the Topcon TRC-F and by vitreous fluorophotometry 1 hour later. Th fluorophotometric curves were recorded by Polaroid camera. Because the values in the anterio vitreous, near the lens, are variable and influence by fluorescein penetration through anterior routes only the posterior half of the curve was analysed The lower area A as indicated in Fig. 1 was roughl integrated, this value representing a true value of th concentration of fluorescein in the posterior vitreous

The values obtained for these areas in each patien are presented in Table 1. These areas were namec A_0, A_1, A_2, and A_3, according to the occasion o their recording, before the trial, after the first month after the second month, or at the end of the thirc month, respectively.

The mean values of areas 0, 1, 2, and 3 in each group of patients were first compared in order tc detect any general difference in behaviour betweer the 2 groups.

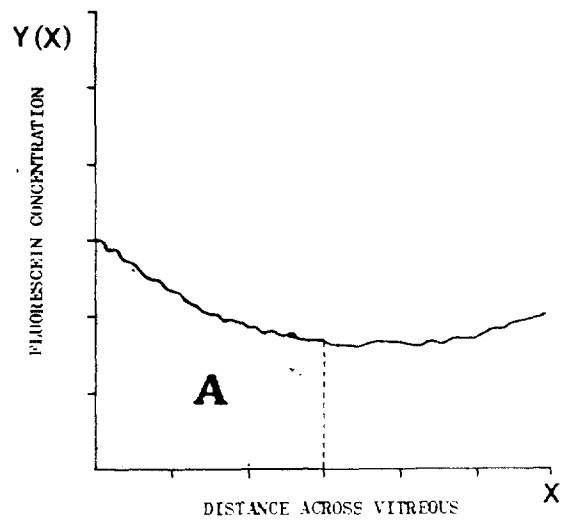


Fig. 1 *Typical fluorophotometric curve. The lower area, A under the curve represents a true value of the concentration of fluorescein in the posterior vitreous*

Table 1 *Values of fluorescein penetration into the posterior vitreous in the 4 examinations during the 3-month trial*

Placebo							*Cyclandelate*						
S. No.	*Age/Sex*	*Fluorescein penetration*				*Clinical information*	*S. No.*	*Age/Sex*	*Fluorescein penetration*				*Clinical information*
		A_0	A_1	A_2	A_3				A_0	A_1	A_2	A_3	
1	60/F	6·1	7·3	9·2	9·2		2	59/F	3·7	6·7	8·3	7·5	
4	50/F	5·4	4·1	6·9	7·0		3	80/F	9·3	9·4	11·9	10·2	
6	47/M	4·4	4·0	6·6	5·9		5	51/F	4·8	5·9	9·4	9·7	
8	42/F	3·3	6·7	5·7	8·4		7	55/M	4·6	6·3	9·1	9·1	Minimal hard exudates
9	33/F	6·7	6·5	6·6	6·9		10	26/F	5·4	7·9	4·7	4·8	
12	68/M	7·5	7·6	8·4	9·6		11	57/M	6·2	6·0	7·1	4·9	
15	64/F	5·9	5·9	9·2	10·3	Minimal hard exudates	16	42/F	7·8	6·0	7·0	5·4	
18	44/M	4·4	4·0	5·5	5·5		17	66/F	4·7	7·0	8·2	8·2	
20	46/F	3·6	6·8	10·2	9·1		19	60/F	4·6	6·1	7·6	6·5	
21	49/M	1·7	3·7	5·3	7·6	Hard exudates; signs of leakage on angiography	22	50/F	2·2	3·6	7·5	4·9	
26	42/F	4·8	4·0	8·7	10·0	Signs of leakage on angiography	25	61/F	6·0	6·4	7·7	6·7	
Mean		4·89	5·51	7·48	8·14				5·39	6·48	8·05	7·08	

The parameter that was used to test efficacy of the drug *v.* the placebo was the difference between the fluorescein concentrations in the posterior vitreous at the final examination, represented by A_3, and the fluorescein concentrations at the previous visits (A_2, A_1, and A_0).

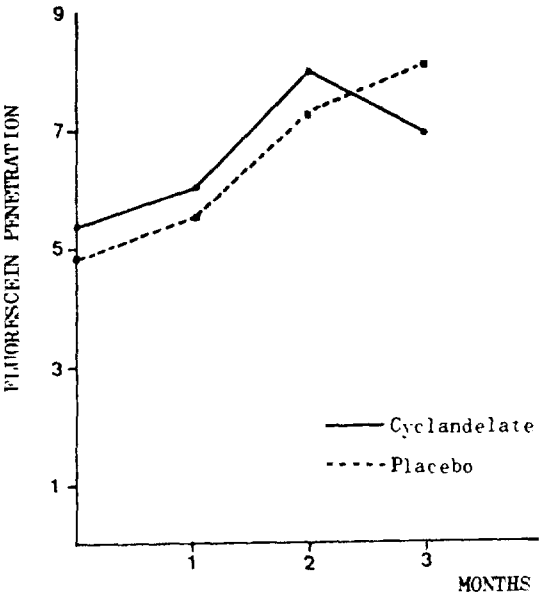
For each patient (11 drug, 11 placebo) these differences ($A_3 - A_0$, $A_3 - A_1$, and $A_3 - A_2$) were subjected to statistical analysis. A final complementary analysis was made taking into account simultaneously for each patient, the differences $A_1 - A_0$ and $A_3 - A_2$, in order to highlight the corrective action of the drug on the abnormal permeability of the blood-retinal barrier. $A_1 - A_0$ represents the natural evolution of the disease, the effect of treatment being then minimal; $A_3 - A_2$ represents best the effect of treatment.

The following standard statistical methods were used: Student's *t* test and standard deviation.

CLINICAL ASSESSMENT

The visual acuity was tested for each patient and he was examined 4 times by ophthalmoscopy, during the course of the trial, at the beginning and at the end of each month.

Fig. 2 *Patterns of fluorescein penetration into the posterior vitreous, in placebo and cyclandelate treated patients, during the 3-month trial*



Results

Assessment of the permeability of the blood-retinal barrier by vitreous fluorophotometry

The mean values of the areas under the fluorophotometric curves, representing the fluorescein penetration into the posterior half of the vitreous, obtained from each patient (11 placebo, 11 cyclandelate) and from the 4 examinations were graphically plotted (Fig. 2). The figure shows a well-defined pattern of progressive increase in the permeability of the blood-retinal barrier, well evidenced by the increased fluorescein penetration into the vitreous, in the placebo-treated patients, during the 3-month period of the trial. This pattern appeared, however, to be completely inverted during the third month of treatment in the patients receiving cyclandelate, suggesting a definite improvement in the conditions of abnormal permeability of the blood-retinal barrier which characterises the early stages of retinal involvement in diabetes.

Table 2 *Differences in fluorescein penetration into the posterior vitreous between the last (A_3) and the initial examination (A_0)*

Placebo		Cyclandelate	
Series No.	$A_3 - A_0$	Series No.	$A_3 - A_0$
1	−3·1	2	−3·8
4	−1·6	3	−0·9
6	−1·5	5	−4·9
8	−5·1	7	−4·5
9	−0·2	10	−0·6
12	−2·1	11	−1·3
15	−4·4	16	−2·4
18	−1·1	17	−3·5
20	−5·5	19	−1·9
21	−5·9	22	−2·7
26	−5·2	25	−0·7
Mean	−3·2		−1·6
±SD	±0·616		±0·736

$t = 1{\cdot}74$; DF = 20; $0{\cdot}1 < P > 0{\cdot}05$.

Table 4 *Differences in fluorescein penetration into the posterior vitreous between the end of the trial (A_3) and the end of the second month (A_2)*

Placebo		Cyclandelate	
Series No.	$A_3 - A_2$	Series No.	$A_3 - A_2$
1	0	2	−0·8
4	−0·1	3	−1·7
6	−0·7	5	−0·3
8	−2·7	7	0
9	−0·3	10	−0·1
12	−1·2	11	−2·2
15	−1·1	16	−1·6
18	0	17	0
20	−1·1	19	−1·1
21	−2·3	22	−2·6
26	−1·3	25	−1·0
Mean	−0·65		−0·96
±SD	±0·357		±0·298

$t = 3{\cdot}6$; DF = 20; $0{\cdot}005 < P > 0{\cdot}001$.

This finding is substantiated when the differences in fluorescein concentration in the posterior vitreous between the last and the previous visits were analysed and the values obtained from patients given placebo capsules compared with the values obtained from cyclandelate-treated patients. The differences in fluorescein penetration, i.e., breakdown of the blood-retinal barrier, between the last visit (A_3) and the initial examination (A_0) are significantly different at the 10% level between the 2 groups of patients, placebo and cyclandelate ($t = 1{\cdot}74$; DF = 20; $0{\cdot}1 < P > 0{\cdot}05$; Table 2).

This level of significance increases, however, when the differences in fluorescein penetration are taken between the last visit and the second and third examinations, after 1 and 2 months of treatment, respectively. The differences between the last visit and the second examination ($A_3 - A_1$), between the 2 groups of patients, are significant at the 2% level ($t = 2{\cdot}7$; DF = 20; $0{\cdot}02 < P > 0{\cdot}01$; Table 3). Finally,

Table 3 *Differences in fluorescein penetration into the posterior vitreous between the end of the trial (A_3) and the end of the first month (A_1)*

Placebo		Cyclandelate	
Series No.	$A_3 - A_1$	Series No.	$A_3 - A_1$
1	−1·9	2	−0·8
4	−2·9	3	−0·8
6	−1·9	5	−3·8
8	−1·7	7	−2·8
9	−0·4	10	−3·1
12	−2·0	11	−1·1
15	−4·4	16	−0·6
18	−1·5	17	−1·2
20	−2·3	19	−0·4
21	−3·9	22	−1·3
26	−6·0	25	−0·3
Mean	−2·6		−0·6
±SD	±0·475		±0·534

$t = 2{\cdot}7$; DF = 20; $0{\cdot}02 < P > 0{\cdot}01$.

the differences between the final observation and the third examination ($A_3 - A_2$) show a highly significant difference between the 2 groups of patients ($t = 3{\cdot}6$; DF = 20; $0{\cdot}005 < P > 0{\cdot}001$; Table 4). These results show clearly that cyclandelate has a beneficial effect upon the breakdown of the blood-retinal barrier which is present in the early stages of diabetic retinopathy, preventing its progressive increase, well evidenced in patients receiving placebo capsules. The results indicate also that this beneficial effect is particularly marked after a period of treatment of 2 months. The fact that the full effect of cyclandelate is especially well evidenced in the third month of treatment, in contrast to the first month when its activity appears to be minimal prompted us to compare the differences between the third month of treatment ($A_3 - A_2$) and the first month ($A_1 - A_0$), i.e. $(A_3 - A_2) - (A_1 - A_0)$ between the 2 groups. The statistical analysis of these differences shows a highly significant difference between the 2 groups ($t = 4{\cdot}4$; DF = 20; $P < 0{\cdot}001$; Table 5).

These results indicate clearly that the breakdown of the blood-retinal barrier as evidenced by the degree of abnormal fluorescein penetration into the vitreous suffered a significant decrease in the diabetic patients treated with cyclandelate when compared to the patients submitted to placebo administration, and that this effect is particularly apparent after 2 months of treatment.

CLINICAL ASSESSMENT

The other examinations performed agree, although in a less clear manner, with the fluorophotometric results. As regards the clinical picture, the cases under study are of such nature that only signs of worsening can be accepted as true changes. The visual acuity remained maximal in every patient

Table 5 *Differences in fluorescein penetration between the third month of the trial ($A_3 - A_2$) and the first month ($A_1 - A_0$)*

Placebo				*Cyclandelate*			
Series No.	$A_3 - A_2$	$A_1 - A_0$	*Difference*	*Series No.*	$A_3 - A_2$	$A_1 - A_0$	*Difference*
1	0	−1·2	−1·2	2	−0·8	−3·0	−3·8
4	−0·1	−1·3	−1·2	3	−1·7	−0·1	−1·8
6	−0·7	−0·4	−0·3	5	−0·3	−1·1	−0·8
8	−2·7	−3·4	−0·7	7	0	−1·7	−1·7
9	−0·3	−0·2	−0·5	10	−0·1	−2·5	−2·6
12	−0·6	−0·1	−0·5	11	−2·2	−0·2	−2·0
15	−1·1	0	−1·1	16	−1·6	−1·8	−0·2
18	0	−0·4	−0·4	17	0	−2·3	−2·3
20	−1·1	−3·2	−2·1	19	−1·1	−1·5	−2·6
21	−2·3	−2·0	−0·3	22	−2·6	−1·4	−4·0
26	−1·3	−0·8	−0·5	25	−1·0	−0·4	−1·4
Mean			−0·02				−2·07
SD			±0·302				±0·455

$t = 4·4$; DF = 20; $P < 0·001$.

during the entire trial. Ophthalmoscopically and angiographically, however, slight changes developed in the fundi of 3 patients receiving placebo and in 1 patient receiving cyclandelate (Table 1). These included the development of minimal hard exudates and some angiographical evidence of fluorescein leakage. The angiographical changes were observed in 2 placebo patients at the last examination, whereas the hard exudates were seen with the ophthalmoscope in 3 placebo-treated patients and in only 1 receiving cyclandelate. An overall clinical impression was, therefore, obtained of more marked progression of the retinal involvement in the diabetics not receiving cyclandelate.

SIDE-EFFECTS

Two patients complained of nausea. This was sufficient to provoke in 1 patient discontinuation of treatment and the consequent dropping out of the respective pair and its substitution with a new pair. It is interesting, however, to note that the second patient who complained of nausea was receiving the placebo capsules.

Discussion

The present trial has shown that cyclandelate in doses of 400 mg capsule, 4 times daily, given for a period of 3 months, has significant beneficial effect upon the breakdown of the blood-retinal barrier which is present in the early stages of retinal involvement in diabetes. The use of vitreous fluorophotometry, a clinical quantitative method of evaluation of the permeability of the blood-retinal barrier, allowed the results to be subjected to statistical analysis. This showed that the progressive deterioration of the blood-retinal barrier observed in the diabetic patients receiving placebo capsules during the 3-month trial was arrested in the patients receiving cyclandelate. This beneficial effect of cyclandelate was particularly marked in the third month of treatment, when the levels of breakdown of the blood-retinal barrier decreased significantly, pointing to some recovery of the disease process, and suggesting even better results from prolonged periods of treatment. In a less clear manner the clinical impression obtained from ophthalmoscopy and fluorescence angiography agreed with the results obtained, showing an apparently more rapid progression of the disease in the placebo-treated diabetics. It remains now to be seen if these results can be confirmed by long-term studies and if the progression and development of the full picture of diabetic retinopathy and final loss of vision can be prevented by prolonged treatment with cyclandelate.

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Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol

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Cephalalgia

Diener HC, Föh M, Iaccarino C, Wessely P, Isler H, Strenge H, Fischer M, Wedekind W, Taneri Z. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. Cephalalgia 1996;16:441–7. Oslo. ISSN 0333–1024

Cyclandelate inhibits calcium-induced contraction of vascular smooth muscle cells, platelet aggregation induced by thrombin, platelet-activating-factor and adenosine, and also suppresses a provoked 5HT release from platelets. This pharmacological profile suggests that cyclandelate may have a potential prophylactic effect in migraine. To test this hypothesis, a double-blind multicentre study was performed in 214 patients to investigate the efficacy and tolerability of cyclandelate compared to placebo and propranolol. After a 4-week baseline period, eligible patients (randomization 3 : 2 : 3) were treated for 12 weeks with daily doses of 1.200 mg cyclandelate ($n=81$), placebo ($n=55$) or 120 mg propranolol ($n=78$). The number of migraine attacks (≥50% responders) and the migraine duration/month were compared based on the difference between baseline and the last 4 weeks of prophylactic treatment. The percentage of patients with a reduction in migraine attacks of ≥50% treated with cyclandelate (37.0%) or propranolol (42.3%) was not significantly superior to placebo (30.9%; $p>0.025$). The mean duration of migraine in hours (h) per month decreased in both active treatment groups (cyclandelate: 36.8 h, $p=0.046$; propranolol: 34.4 h, $p=0.039$) compared to placebo (13.7 h) without reaching statistical significance ($\alpha/2=0.025$). The clinical efficacy of cyclandelate and propranolol was comparable. Adverse experiences were reported by 13 patients (16.0%) treated with cyclandelate, by 5 patients (9.1%) treated with placebo and by 19 patients (24.4%) treated with propranolol. These were drug-related in 7.1% ($n=6$) of patients treated with cyclandelate and in 9% ($n=7$) of patients treated with propranolol. In summary, cyclandelate has a comparable efficacy to that of propranolol, an established drug of first choice in the prophylaxis of migraine. Both drugs were better than placebo, but not significantly so. Both active treatments were well tolerated. □ *Cyclandelate, double-blind, placebo, propranolol, prophylaxis of migraine, tolerability*

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Patients with frequent, prolonged and severe migraine attacks require migraine prophylaxis. A reduction in the frequency of attacks and the duration of migraine are two important aims. The mode of action of most drugs used in migraine prophylaxis is not known. Furthermore, no animal models are available to establish the mode of action of these medications. The prophylactic effect of beta-blockers, the most widely used drugs in the prophylaxis of migraine, was discovered by chance in patients treated for hypertension who at the same time suffered from migraine. Propranolol (1–6) has convincingly been shown to have migraine prophylactic activity. This activity has been confirmed by Holroyd et al. (7), who performed a meta-analysis of studies on propranolol in the prophylaxis of migraine. The 53 studies included 2403 patients who were treated with the beta-blocker propranolol (medium standard dose 160 mg/day) versus reference substances or placebo. On average, propranolol resulted in a 44% reduction in migraine activity when daily headache recordings were used to assess treatment outcome and in a 65% reduction of migraine activity when less conservative measures (e.g. clinical ratings of improvement, global patient reports) were used. The dropout rate due to side effects was 5.3%.

Cyclandelate inhibits provoked calcium overload in neurons (8), calcium-induced contraction of

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vascular smooth muscle cells (9–10), and platelet aggregation induced by thrombin, platelet activating factor (PAF) and adenosin (11). In addition, cyclandelate inhibits a provoked 5HT release from platelets (11–13) and protects against provoked cortical damage in a mouse model of focal ischaemia (14). This pharmacological profile suggests the likelihood of a prophylactic activity in migraine.

Earlier studies have indicated that cyclandelate given at a daily dosage of 1600 mg indeed has an anti-migraine prophylactic effect. In a small pilot trial ($n=40$), Nappi et al. (15) showed that cyclandelate was almost equally effective to flunarizine. Mastrosimone et al. (16) ($n=84$) described a significant superiority of cyclandelate to pizotifen. Gerber et al. (17) ($n=84$) observed a clinically relevant decrease in migraine symptoms with cyclandelate which was comparable to that of propranolol. Cyclandelate was well tolerated in all efficacy studies and exhibited the smallest incidence of adverse events compared to the reference drugs used (15–18).

Methods

To test the hypothesis that cyclandelate is more effective than placebo in the prophylaxis of migraine using the minimal effective dosage of 1200 mg/day, a randomized, parallel-group, double-blind multicentre study was performed. As a secondary hypothesis, comparative efficacy with propranolol (120 mg/day) was investigated. The study was approved by the respective local ethics committees.

Inclusion criteria

Patients between the age 18 and 60 years; male or female; migraine with and/or without aura according to the IHS criteria (19); migraine history of at least 12 months' duration; a mean number of 2–10 migraine attacks per month within the last 3 months prior to the study; and signed informed consent were admitted to the study.

Exclusion criteria

Pregnant or lactating women; psychiatric disorders; concomitant non-migraine headaches ≥3 times per month within the last 3 months; intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks preceding the trial; specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder); intake of drugs to treat migraine attacks>12 days/month. Prior to study entry and at the end of the treatment, the patients underwent physical and neurological examinations, including ECG and blood chemistry tests.

Design

Patients who fulfilled the entry criteria entered a 4-week baseline period without any prophylactic treatment. Those who recorded 2–10 attacks on their migraine headache diaries during the baseline period qualified for randomization (randomization ratio= 3 : 2 : 3) to cyclandelate, placebo or propranolol. To avoid early withdrawals due to initial side effects, treatment started with a 2-week run-in period at a dosage of 400 mg tid cyclandelate placebo or 40 mg tid propranolol. This was followed by a 12-week period of active prophylaxis at a dosage of 400 mg tid cyclandelate, placebo or 40 mg tid propranolol. The study ended with a 2-week run-out period to avoid early recurrence of migraine, using the same dosages as in the run-in period. Additional medication to treat acute migraine attacks was allowed for up to 12 days/month for the duration of the study, including the baseline period. Patients were required to come for a check-up visit at the end of the baseline period and at weeks 10, 14, 18 and 20 (Fig. 1).

Migraine headache diary

All patients kept a structured weekly diary and recorded daily migraine events: occurrence of migraine attacks; impairment of working ability; intensity of headache (measured by a visual analogue scale); duration of headache and migraine attack; intake of migraine medication during the attack; concomitant symptoms of migraine (e.g. photo- or phonophobia, nausea, autonomic disturbances, etc.). Patients were also asked to record adverse events related to the prophylactic medication. The attending physician was requested to transcribe the frequency and duration of migraine attacks and adverse events in the Case Report Forms (CRFs) at each visit.

Analysis of diaries

At the end of the study and prior to breaking the code, the attending physician evaluated all migraine headache diaries, blinded to the number and total duration of migraine attacks at baseline and in the last 4 weeks of prophylaxis. This diary database was used for primary analysis applying the following guidelines: (a) If migraine attacks occurred on two consecutive days within a time interval of less than 24 h, this was counted as one migraine attack; (b) the migraine duration was defined as the sum of all migraine hours documented by the patient in the diary within the 28 days preceding the end of baseline (week 4) and prophylactic treatment visits (week 18) (Fig. 1); (c) in cases where the patient was

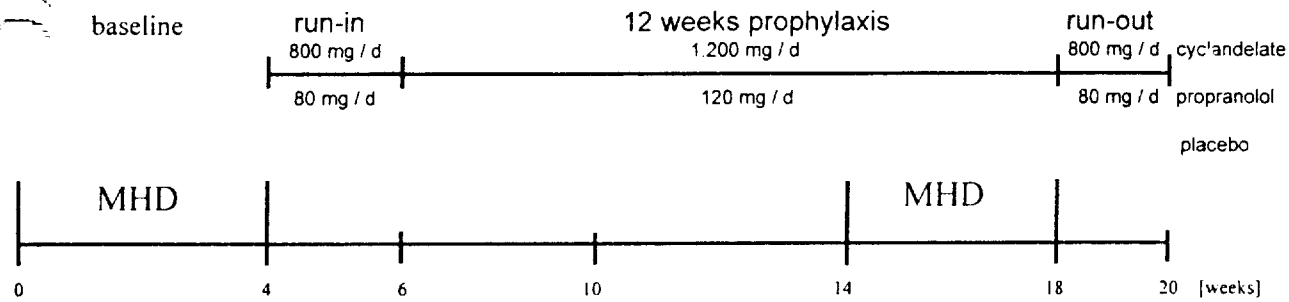

Fig. 1. Time course of the study, dosages and migraine evaluation.

run-in/run-out 2 weeks: cyclandelate 400 mg bid vs placebo vs propranolol 40 mg bid: 1-0-1 capsules/day
prophylaxis 12 weeks: cylandelate 400 mg tid vs placebo vs propranolol 40 mg tid: 1-1-1 capsules/day
MHD Migraine headache diary: evaluation 4 weeks baseline vs last 4 weeks of prophylaxis
1 ... 20 weeks scheduled check-up visits.

not able to distinguish between migraine and tension-type headaches, all additional concomitant symptoms documented in the diary were taken into consideration.

Endpoints and statistics

Two equivalent primary endpoints were defined: (a) "rate of responders", i.e. patients with ≥50% reduction in the number of migraine attacks; (b) mean "migraine duration" in hours. The migraine parameters were calculated using the values of the last 4 weeks of the high-dosage period compared to those of the 4-week baseline period. Efficacy was assumed if cyclandelate showed significant superiority to placebo at an alpha-adjusted two-sided significance level of $\alpha/2=0.025$ in at least one of the two target criteria. Fisher's exact test and the *t*-test for independent samples were used as statistical methods for the rate of responders and migraine duration, respectively. Two patient populations were defined for statistical analysis, all randomized patients (intention-to-treat [ITT] group) and clinically relevant patients (per protocol [PP] group). All drop-outs after baseline were included in the intention-to-treat analysis on the basis of the last-value-carried-forward method.

Secondary endpoints were the efficacy of propranolol versus placebo and equivalent efficacy of cylandelate compared to propranolol. Additional secondary endpoints were change in intensity of headache, intake of analgesics or migraine drugs, number of working days lost due to migraine, frequency and severity of adverse events. For the secondary endpoints, adverse events and intake of acute migraine medication, only posthoc analyses are presented.

Case number of patients

Assuming a 60% response rate with cyclandelate and 30% with placebo and a reduction in migraine duration of 4 h with placebo and 8 h with cyclandelate with a standard deviation of 6 h, the sample size for cyclandelate and propranolol was calculated at $n=75$ and $n=50$ for placebo in the randomization ratio of 3 : 2 : 3. These case numbers are sufficient to find a statistically significant difference between cyclandelate (or propranolol) and placebo at $\alpha/2=0.025$ with a beta error of 20%.

Post-hoc analysis

The intake of medication to treat acute migraine attacks is known to be an accompanying critical issue for the evaluation of headache duration in clinical trials for prophylactic treatment. Therefore, all patients were stratified based on the intake of analgesics/antimigraine drugs during a defined number of weeks in the course of the trial. To obtain new insight into possibly different response properties of the ITT patient database, the ≥50% response criterion reduction of migraine duration was combined with the criterion "intake of acute medication over less than 5 weeks" during the 16 weeks of treatment (double response criterion).

Results

Study population

The study was initiated in November 1991 and finished in April 1994. Twenty-one screened patients did not qualify for randomization. A total of 214 ITT patients in 17 centres were randomized after completing the baseline period, 81 patients (37.9%) were treated with cyclandelate, 55 (25.7%) with placebo and 78 (36.4%) with propranolol. Forty patients had to be excluded from the ITT analysis for various reasons (Table 1) and 174 patients (cyclandelate $n=67$, placebo $n=39$, propranolol $n=68$) remained for the PP analysis.

Table 1. Patients violating protocol requirements.

Reasons for exclusion from ITT database	$n=40$
Early study termination/not drug-related	$n=15$
≤2 attacks during baseline period (one <24 h)	$n=8$
Evaluation of diary not possible	$n=7$
Control visit missed by >2 weeks	$n=6$
Intake of additional medication ≥15 days/4 weeks	$n=2$
Age <18 or >60 years	$n=2$

Demographic and baseline data (Table 2)

The three treatment groups were comparable in terms of age, distribution of gender and history of migraine (Table 2). The three treatment groups were comparable with regard to number of attacks/4 weeks, intensity of pain during attacks and intake of acute migraine medication. The mean duration of migraine in hours/4 weeks and the standard deviation was slightly greater in the cyclandelate group than in the placebo and propranolol groups. However, the differences did not reach statistical significance.

Withdrawals after randomization

Thirty-six patients (16.8%) dropped out after randomization (cyclandelate $n=16$, placebo $n=8$, propranolol $n=12$). The frequency of withdrawals under cyclandelate and propranolol was comparable, but numerically higher compared to placebo in the efficacy-related and possibly drug-related reasons. The overall distribution of all reasons for withdrawals is given in Table 3.

Efficacy

Primary endpoints

The first primary endpoint (≥50% reduction of migraine attacks) was met by 30/81 (37.0%) patients treated with cyclandelate and 17/55 (30.9%) patients treated with placebo. There was no significant difference between the two groups ($p>0.025$). In the propranolol group the response criterion was fulfilled by 33/78 (42.3%, $p>0.05$ vs placebo) patients. Similar results were obtained for the per protocol analysis (Fig. 2).

The mean absolute reduction of migraine duration/4 weeks (second primary endpoint) was 36.8±73.7 h with cyclandelate compared to

Table 2. Comparison of the three treatment groups.

Patient characteristics	Total $n=214$	Cyclandelate $n=81$	Propranolol $n=78$	Placebo $n=55$
Demographic and baseline data				
Mean age (years)	39±12	39±12	40±13	39±11
Sex				
Women	167/78.0%	66/81.5%	60/76.9%	41/74.5%
Men	47/22.0%	15/18.5%	18/23.1%	14/25.5%
Mean migraine history since (years)	19±12	18±12	21±13	19±11
Migraine with aura	56/26.2%	24/29.6%	18/23.1%	14/25.5%
Migraine without aura	156/72.9%	56/69.1%	59/75.6%	41/74.5%
Migraine with + without aura	2	1	1	0
No. of patients with acute migraine medication:				
Analgesics/antirheumatics	142/66.4%	55/67.9%	51/65.4%	36/65.5%
Specific migraine drugs	127/59.3%	46/56.8%	49/62.8%	32/58.2%
		Cyclandelate	Propranolol	Placebo
Migraine baseline data				
Mean number of attacks/4 weeks		4±1	4±2	4±2
≤4 attacks		3±1	3±1	3±1
Mean migraine duration/4 weeks (h)		88±79	81±50	73±41
≤4 attacks		81±79	69±46	71±42
Pain intensity during attack				
Severe		27/33.3%	26/33.3%	17/30.9%
Moderate		51/63.0%	49/62.8%	31/56.4%
Mild		3/3.7%	3/3.8%	7/12.7%
Additional medication during attacks				
Never		6/7.4%	3/3.8%	2/3.6%
Sometimes		23/28.4%	24/30.8%	15/27.3%
Every attack		52/64.2%	51/65.4%	38/69.1%

le 3. Reasons for withdrawal

Reason No. of patients (%)	Total $n=214$ $n=36$ (16.8%)	Cyclandelate $n=81$ $n=16$ (19.8%)	Propranolol $n=78$ $n=12$ (15.4%)	Placebo $n=55$ $n=8$ (14.4%)
Not drug-related	15 (7.0%)	5 (6.2%)	3 (3.8%)	7 (12.7%)
Efficacy-related (total)	8 (3.7%)	5 (6.2%)	3 (3.8%)	–
Complete relief	2 (0.9%)	2 (2.5%)	–	–
Lack of efficacy	6 (2.8%)	3 (3.7%)	3 (3.8%)	–
Adverse events (no. of patients)	13 (6.1%)	6 (7.4%)	6 (7.7%)	1 (1.8%)
Side effects	9 (4.2%)	5 (6.2%)	4 (5.1%)	–

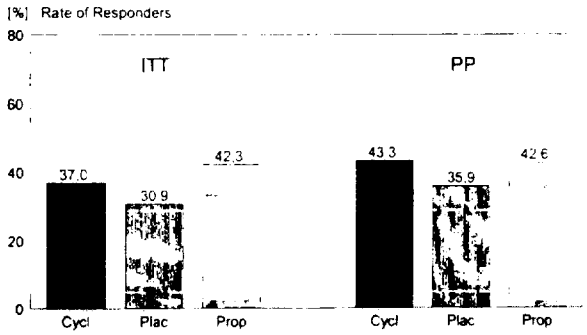

Fig. 2. Rate of responders (≥50% reduction of attack frequency/4 weeks) compared to baseline.

=Intention-to treat PP=per Protocol
l=cylandelate Plac=placebo Prop=propranolol
$^*p>0.05$; $\alpha/2=0.025$ (Fisher's exact test, 2-sided).

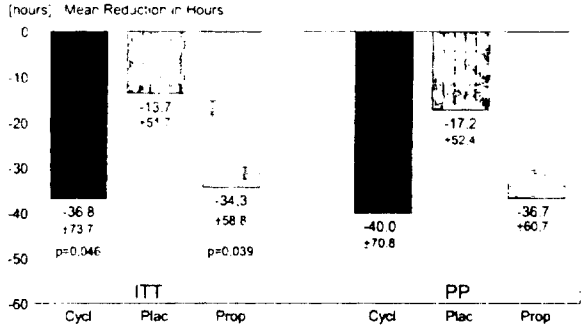

Fig. 3. Mean absolute reduction of migraine duration/4 weeks compared to baseline.

ITT=Intention-to treat PP=per Protocol
Cycl=cyclandelate Plac=Placebo Prop=Propranolol
$^*p>0.05$; $\alpha/2=0.025$ (*t*-test for independent samples, 2-sided.

13.7±51.7 h with placebo ($p=0.046$). Propranolol reduced the migraine duration on average by 34.6±58.8 h ($p=0.039$). These results were clinically relevant for both active drugs, but failed to achieve the adjusted significance level of $\alpha/2=0.025$ (ITT). Similar results were obtained for the per protocol analysis (Fig. 3).

Secondary endpoints

Equivalence of cyclandelate and propranolol. No significant statistical equivalence of cyclandelate and propranolol was found in either main efficacy criteria ($p=0.05$, 1-sided).

Post hoc analysis

The analysis of the subgroup of patients that fulfilled the response criterion of a ≥50% reduction of migraine duration with an intake of acute medication over less than 5 weeks during the course of e study showed cyclandelate to be significantly perior to placebo (32.1% vs 12.7%, $p=0.014$) in ntrast to propranolol (19.2%, $p>0.05$). The analysis of the complementary responder groups with an intake of acute medication during more than 5 weeks did not show any significant difference between placebo and active drug.

The 1-sided equivalence test showed significant equivalence of cyclandelate and propranolol in the reduction of migraine duration (32.1% vs 19.2%, $p=0.007$).

Tolerability/side effects

Blood pressure and blood chemistry remained unchanged throughout the trial in all three treatment groups. In the propranolol group the heart rate was reduced on average by 5 beats/min. Thirteen of 81 (16.0%) patients treated with cyclandelate, 5 of 55 (9.1%) patients with placebo and 19 of 78 (24.4%) patients with propranolol reported adverse events. Of these adverse events, a total of 16 events in 13 patients were probably drug-related side effects (Table 4). Five patients in the cyclandelate group and 4 patients in the propranolol group withdrew from the study due to side effects.

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